American Heart Journal

VOL. 28 DECEMBER, 1944 NO. 6

Original Communications

SYNCOPE ASSOCIATED WITH EXERTIONAL DYSPNEA AND ANGINA PECTORIS

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IT IS well known that recurrent attacks of syncope occur in association with aortic stenosis and in disorders of the intracardiac conduction mechanism (Adams-Stokes syncope). Little attention has been paid, however, to the occurrence of syncope and periods of mental confusion in patients with other common forms of heart disease. Any type of heart disease that produces acute paroxysmal dyspnea and anginal pain may be associated with periods of unconsciousness.

As will be noted, the attacks of syncope experienced by the patients reported here were associated with both paroxysmal dyspnea and the appearance of characteristic angina pectoris. This syndrome was first described by Gallavardin,[1] who gave it the name "syncope anginosa." Patients with heart disease are usually limited in their activities by one of two factors. Either dyspnea appears when the left ventricle is unable to remove blood from the pulmonary circuit, or angina pectoris results from focal ischemia due to inability of the coronary arteries to supply an adequate amount of blood to the myocardium. Which symptom is the limiting factor during exertion depends on the relative efficiency of the myocardium and the coronary circulation. It is not uncommon for patients to have first one symptom, and then, at a later date, the other. This is particularly striking when angina pectoris disappears after myocardial infarction, and is supplanted by dyspnea as the limiting symptom. There are patients, however, in whom the coronary circulation and the ventricular output "fail" at the same level of exertion, and who complain of both dyspnea and angina pectoris. The cases under consideration fall into this group. The significance of these factors in the production of syncope will be discussed later.

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Received for publication Dec. 6, 1943.

CASE REPORTS

CASE 1.—W. E. W., aged 61 years in 1941, was admitted to the hospital because of anginal pain, syncope, and paroxysmal nocturnal dyspnea. In 1940, a year and a half before entry, he began to experience substernal and precordial pain, "knifelike" in character, produced by exertion, and relieved by rest and the administration of nitroglycerin. At about the same time, he noted frequent attacks of paroxysmal nocturnal dyspnea. Six weeks before admission, during exertion, he suddenly noted a "fluttering" of the heart, followed shortly by severe dyspnea and "drilling" precordial pain. A minute later he lost consciousness, and remained unconscious for several hours. He awoke feeling very "limp." During the six weeks before admission, he had experienced numerous similar attacks of angina, "fluttering," and dyspnea, produced by exertion, and followed by sudden syncope unless he was able to lie down or gain support. He also had many attacks of severe nocturnal dyspnea and angina, but no syncope.

Physical examination revealed a large, obese man with marked orthopnea. There were mild tortuosity and arteriovenous nicking of the retinal arterioles. There were a few moist râles at the bases of both lungs. The heart was slightly enlarged to the left. The sounds were of poor quality, and there was a grade 1 apical systolic murmur. The rhythm was normal. Marked hepatomegaly was present; the edge of the liver was palpable 10 cm. below the costal margin. The extremities and reflexes were normal. The blood pressure was 134/90. Carotid sinus stimulation and forced hyperventilation produced no abnormal effects.

The urine was normal except for 1 plus proteinuria on two occasions. The erythrocyte count was 6.2 million, with a hemoglobin content of 16.8 Gm. per 100 cubic centimeters. The sedimentation rate was normal. The blood Hinton and Wassermann reactions were negative. The leucocyte count was 9,600. The icterus index, total protein, nonprotein nitrogen, and bromsulfalein excretion were within normal limits.

Roentgenologic examination of the heart showed slight prominence of the left ventricle and tortuosity of the aorta. Electrocardiograms showed only T-wave inversion which was probably a digitalis effect.

Comment.—This patient experienced numerous attacks of exertional dyspnea, angina pectoris, and sudden syncope during the six weeks prior to hospital admission. He had had symptoms of heart disease for one and one-half years. The clinical diagnosis was arteriosclerotic heart disease and hepatomegaly of unknown origin.

CASE 2.—M. L. H., aged 38 years in 1943, was found to have a positive serologic test for syphilis in 1934. In June, 1939, she first noted attacks of exertional dyspnea, and angina pectoris characterized by "mashing" substernal pain radiating down the left arm. These attacks became more frequent, and she also noted orthopnea, paroxysmal nocturnal dyspnea, and intermittent edema of the ankles. She had experienced about fifteen attacks of syncope during this period. A typical attack was described as the sudden appearance of shortness of breath during exertion, followed by anginal pain. In a few seconds she would lose consciousness for a period of from five minutes to as long as an hour. When she regained consciousness, the substernal pain often persisted for five or ten minutes, but was much milder.

She always felt cold and clammy after an attack, and had vomited on several occasions.

Physical examination showed a well-developed and well-nourished Negro woman. The blood pressure was 110/80. The optic fundi and the lungs were normal. The heart was slightly enlarged to the left. No murmurs were heard and the rhythm was regular. The pulmonic second sound was louder than the aortic second sound. The liver was palpable 2 cm. below the costal margin. The extremities and reflexes were normal. Neither carotid sinus stimulation nor hyperventilation produced syncope.

The urinalysis was negative. The erythrocyte count was 4.2 million, with a hemoglobin content of 13.5 Gm. per 100 cubic centimeters. The sedimentation rate was 23 mm. per hour. The leucocyte count was 8,100.

Roentgenologic studies of the heart showed slight left ventricular enlargement. Electrocardiograms showed left axis deviation, a deep S_3, an inverted T_3, and a slightly elevated $S\text{-}T_4$.

Comment.—This patient gave a history of numerous attacks of dyspnea, angina pectoris, and prolonged unconsciousness, brought on by exertion during the four years before admission to the hospital. The clinical diagnosis was probable coronary ostial disease due to syphilitic aortitis.

CASE 3.—W. T. M., aged 57 years in 1942, was admitted to the hospital complaining of attacks of angina pectoris and syncope. Four years before admission he was found to have hypertension, and, shortly thereafter, he began to experience exertional dyspnea and paroxysmal nocturnal dyspnea. These symptoms became marked. About six months later, he started having attacks of angina pectoris and syncope. Dependent edema developed two months before entry. The patient claimed he had had "hundreds" of syncopal attacks associated with exertion. These attacks started with severe shortness of breath and a feeling of being "choked-up." In a few seconds, or, at most, a minute, he was seized by "stabbing" substernal pain radiating down both arms as far as the elbows. Then, "everything went black," and he would lose consciousness for a period of several minutes to as long as an hour. He was able to tell when syncopal attacks were imminent, and avoided injury by lying down quickly. Syncope had never occurred at night. It was always preceded by angina.

Physical examination revealed a well-developed, obese man with marked orthopnea. His blood pressure was 210/100. The retinal arterioles showed moderate arteriosclerotic changes, with arteriovenous compression, but no hemorrhages or exudates. The heart was enlarged to the left. There was a rough, grade 2, systolic murmur, heard best over the third left intercostal space, but heard well over the entire precordium. The murmur was not transmitted to the neck vessels. The aortic second sound was sharp, and louder than the pulmonic second sound. The edge of the liver was palpable two fingerbreadths below the costal margin. There was marked edema of the lower extremities.

The urine was normal. Blood studies showed an erythrocyte count of 4 million, with a hemoglobin content of 10.2 Gm., a sedimentation rate of 55 mm. per hour, and a leucocyte count of 5,200. The blood Kahn reaction was negative.

Fluoroscopic examination showed definite left ventricular enlargement and tortuosity of the thoracic aorta, but no areas of intracardiac calcification. The electrocardiogram showed only left axis deviation.

Prolonged carotid sinus stimulation produced transient syncope. There was marked hyperpnea before recovery of consciousness. He then complained of mild chest pain, and stated that he felt as if he had been unconscious for several hours. An electrocardiogram taken during carotid sinus stimulation showed complete auriculoventricular block and marked slowing of the auricular rate.

Hyperventilation produced mild anginal pain, but no syncope.

Comment.—The clinical diagnosis was hypertensive heart disease and generalized arteriosclerosis. The patient gave a history of many attacks of syncope, preceded by exertional dyspnea and angina pectoris. Although syncope could be produced by prolonged carotid sinus stimulation, this syncope was subjectively different from the attacks previously experienced.

CASE 4.—H. G. N., aged 58 years in 1942, began having exertional dyspnea and edema of the ankles in 1933. Shortly thereafter, he noted attacks of angina pectoris. Orthopnea appeared in 1934, and paroxysmal nocturnal dyspnea in 1937. Exertion usually produced shortness of breath. However, he was often forced to stop activity by angina without dyspnea, although the latter usually appeared shortly thereafter. The angina was described as a "knifelike" pain radiating from the substernal region to the left axillary line in the fourth intercostal space, and was relieved by rest or nitroglycerin. In 1937, the patient had a sudden attack of syncope which occurred while sitting. It was not preceded by dyspnea. He stated he was unconscious for twenty-four hours. After this he had five attacks of syncope associated with exertion. All occurred when his cardiac function was poor, as evidenced by marked exertional dyspnea and peripheral edema. The attacks started with sudden, severe dyspnea, followed by anginal pain. Syncope then occurred without warning. He would remain unconscious for a period of several minutes to several hours. On innumerable occasions he had attacks of sudden dyspnea and angina, and "felt funny all over," but prevented syncope by sitting down immediately.

He was seen in the hospital after three of these syncopal attacks. On these occasions he showed evidence of marked congestive heart failure, and was either comatose or irrational. The temperature remained normal, as did the leucocyte count and sedimentation rate. Electrocardiograms showed no evidence of myocardial infarction.

Physical examination in October, 1942, revealed a blood pressure of 240/140. There was marked peripheral arteriosclerosis, and the retinal arterioles showed moderate tortuosity and arteriovenous compression. The lungs were normal. The heart was at the upper limits of normal size. The rhythm was regular and no murmurs were heard. The abdomen was negative. All of the reflexes were normal. Carotid sinus stimulation was without effect. Forced hyperventilation produced only "tingling" of the extremities.

Roentgenologic examination of the heart showed an aortic configuration and a tortuous aortic arch. Electrocardiograms showed only an abnormality of the T waves which was probably a digitalis effect.

Comment.—This patient had hypertensive heart disease and generalized arteriosclerosis. He had had exertional dyspnea and angina pectoris for nine years. He had had one attack of sudden syncope unassociated with exertion or dyspnea, but after this had five attacks of acute exertional dyspnea, angina, and syncope.

CASE 5.—J. W. C., aged 64 years in 1942. At the age of 32 years, during extreme exertion, the patient was suddenly struck with severe precordial pain accompanied by a cold sweat and prostration. An hour later, the pain radiated down the left arm. It was sharp, "stabbing," and intermittent; numbness of the same area at times replaced the pain. These symptoms continued for about fifteen hours. Ever after this attack the patient complained of frequent attacks of severe substernal pain radiating down the left arm. At first they were produced only by exertion, but, during the several years preceding admission, they had occurred when sitting or lying down. The pain would last three to five minutes, and was relieved by rest. In 1942, the patient had five attacks of very severe paroxysmal nocturnal dyspnea, occurring at times when cardiac decompensation was most marked. He was awakened by "suffocating" dyspnea. He would sit up or try to walk to a window. Immediately, the sharp substernal pain would appear. It would last about five minutes, and often reappear after a few minutes. His body then felt "numb all over." He would have only partial recognition of his surroundings, and felt as if he were "dreaming," but he did not believe he had ever lost consciousness. This state would persist for about one hour. As he became mentally clear, the chest pain would occasionally reappear in milder form.

The patient gave a history of a penile lesion in 1902, and had received antisyphilitic treatment by mouth for four years.

Physical examination revealed moderate retinal arteriosclerosis. The neck veins were distended. The lungs were emphysematous, but no râles were heard. The apex impulse of the heart was in the anterior axillary line in the sixth intercostal space. The rhythm was regular, with a rate of 64. There was a soft, blowing systolic murmur over the entire precordium, and a high-pitched, grade 2, aortic diastolic murmur was heard. The blood pressure was 190/85. There were a Corrigan pulse, a capillary pulse, and marked suprasternal pulsations. The liver was palpable two fingerbreadths below the costal margin. There was slight edema of the ankles. The reflexes were normal. Carotid sinus stimulation produced only slight slowing of the ventricular rate. Hyperventilation resulted in numbness and tingling of the extremities after a short time.

The urinalysis was negative. The hemoglobin content of the blood was 15 Gm. per 100 c.c., and the leucocyte count was 7,000. The blood Kahn reaction was positive.

Roentgenologic examination of the heart showed an aortic configuration, with marked left ventricular enlargement and tortuosity of the aortic arch. Electrocardiograms showed left axis deviation, slurred QRS complexes, a deep S_2 and S_3, and an inverted T_4.

Comment.—The clinical diagnosis was syphilitic aortitis with aortic regurgitation. Although this patient had never experienced actual syncope, he had had five attacks of severe paroxysmal nocturnal dyspnea, with angina pectoris, and marked loss of mental clarity.

CASE 6.—R. L. C., aged 54 years in 1942, had recurrent attacks of acute rheumatic fever as a child, and a further attack of polyarthritis at the age of 35 years. He had had exertional dyspnea for about one year, slight edema of the ankles for eight months, and orthopnea and paroxysmal nocturnal dyspnea for two months. Six months before he was seen, he began having substernal pain radiating to both shoulders and down the left arm, brought on by exertion. These attacks, always preceded and accompanied by marked dyspnea, were associated with "the staggers" and a "faint feeling" lasting about five minutes. He had had no syncope.

Physical examination showed moderate arteriosclerotic changes in the retinal arterioles. The anteroposterior diameter of the chest was increased, with moderate kyphosis. The apex impulse of the heart was in the anterior axillary line in the fifth left intercostal space. A grade 3 systolic murmur and a grade 2 diastolic murmur were heard at the apex. The rhythm was regular, except for occasional extrasystoles, with a rate of 60. The blood pressure was 110/65. There was no peripheral edema. Carotid sinus stimulation and forced hyperventilation produced no abnormal responses.

Fluoroscopic examination of the heart showed left and right ventricular enlargement and dilatation of the left atrium. There was calcification of the mitral valve. Electrocardiograms showed left bundle branch block, with inverted T waves in Leads I, II, and IV.

Comment.—The clinical diagnosis of rheumatic heart disease, with marked mitral stenosis and regurgitation, was confirmed by autopsy in June, 1943. In addition, there were moderate aortic stenosis and slight involvement of the tricuspid valve. Although this patient had never experienced syncope, he had had numerous attacks of dizziness and faintness associated with marked dyspnea and angina pectoris.

DISCUSSION

These patients present certain features in common. The sequence of events leading to syncope was described by them in remarkably the same manner. There was first the appearance of severe dyspnea, almost always associated with exertion. This was followed by true anginal pain, and then, in a matter of seconds, by syncope, unless the patient was able to sit or lie down immediately. This sequence was the same in those patients who described periods of marked impairment of cerebral function, although they did not experience actual syncope. Another feature was that syncope or mental confusion was most likely to occur at times when cardiac decompensation, as judged by exertional dyspnea and peripheral edema, was most marked.

The cause of the heart disease in these patients was varied. The clinical diagnoses were: arteriosclerotic heart disease, coronary ostial disease due to syphilitic aortitis, hypertensive heart disease (two cases), syphilitic aortic regurgitation, and rheumatic heart disease with mitral, and to a lesser degree, aortic stenosis and insufficiency. Varying degrees of congestive heart failure were found at the time of examination. Forced hyperventilation failed to produce syncope in any of the

cases. Carotid sinus stimulation was also without effect, except in Case 3. Here, transient syncope was produced, and electrocardiograms showed complete auriculoventricular block, but the patient stated that this attack was not similar to his previous syncopal attacks. Electrocardiographic studies of the other patients failed to reveal irregularities of rhythm or pacemaker.

The explanation of the periods of unconsciousness in this group of patients is not clear. It might be useful to review some of the common forms of syncope, and to consider these patients in their light.

SYNCOPE OF REFLEX ORIGIN

Syncope can be produced by several reflex mechanisms. The common faint, the syncope caused by certain types of neurogenic heart block, and the mental confusion and syncope secondary to hyperventilation are all reflex in origin.

Fainting occurs in patients with unstable vasomotor centers. The afferent stimuli may arise from the eyes, ears, or nose, from any afferent nerve in the body, or from the emotional content of thought. The efferent limb of the reflex arc may cause syncope by a marked decrease in arterial pressure secondary to either venous pooling or arteriolar dilatation, or, more rarely, by ventricular standstill secondary to sinoauricular or auriculoventricular block. In certain cases, both afferent and efferent limbs of the reflex arc are in the vagus nerve (so-called vagovagal syncope). The afferent impulses, which may arise in the pharynx, the bronchial mucosa, the esophagus, the stomach, and the mediastinum, cause syncope by sinus bradycardia or by sinoauricular and auriculoventricular block.

Was the syncope in the cases reported here similar to that of the common fainting attack? Patients who faint frequently give a history of previous attacks of syncope. Maloney,[2] in a study of syncopal attacks in blood donors, has pointed out that persons with a history of fainting are much more likely to lose consciousness than those who give no history of previous faints. Fainting is much more likely to occur when the patient is standing still than when he is active. The patients with heart disease described here gave no history of fainting before the onset of cardiac decompensation, and the loss of consciousness was precipitated by activity rather than quiet standing. In several cases the unconsciousness lasted for a longer period of time than is usual in simple fainting. Nevertheless, the ischemic myocardium, the congested lungs, and the great veins offer a source of many afferent impulses which might easily precipitate syncope, either by a depressor action on the arterial pressure or by reflex cardiac standstill.

Syncope due to a hyperactive *carotid sinus* reflex is a well-known phenomenon. As pointed out by Weiss,[3] this may occur in three ways:

(1) Stimulation of the sinus may result in reflex slowing of the heart rate and a fall in blood pressure secondary to decreased cardiac output, comparable to Adams-Stokes syncope. This reflex can be abolished by atropine and by epinephrine and ephedrine. (2) There may be a direct fall in arterial pressure, independent of the heart rate. This mechanism is abolished by increasing the peripheral vascular tone with epinephrine or ephedrine, but is not affected by atropine. In both of these types, syncope can be attributed to cerebral "ischemia," or the rapidity of change in cerebral blood flow. (3) Syncope may occur without either a fall in blood pressure or slowing of the heart rate, and with no change in peripheral blood flow per se. This is apparently due directly to cerebral components of the reflex arc.

The appearance of syncope in cases of aortic stenosis has been attributed to involvement of the carotid sinus reflex. Marvin and Sullivan[4] pointed out that syncope was almost always associated with exertion, although the exertion was often quite mild. This relation to exertion and the long duration of the unconsciousness, they felt, ruled out the common faint and some of the common cardiac arrhythmias. One of their patients showed transient auriculoventricular nodal rhythm, ventricular premature contractions, and auricular tachycardia during induced syncope. They hypothesized that increased pressure within the carotid artery secondary to exertion could sufficiently stimulate the carotid sinus to cause reflex syncope, and that the electrocardiographic changes observed in this case were consistent with this form of syncope. Unfortunately, the carotid sinus reflex was not tested in their five cases, and Contratto and Levine[5] were unable to demonstrate abnormal sensitivity of the carotid sinus in nineteen cases of aortic stenosis.

All of the patients under discussion were tested for carotid sinus sensitivity. In one instance (Case 3), prolonged stimulation resulted in transient syncope, and electrocardiograms showed complete auriculoventricular block and slowing of the auricular rate. However, this induced syncope was subjectively unlike the spontaneous attacks he had previously experienced. In none of the other cases was there any significant slowing of the heart rate, or dizziness, weakness, or syncope.

Syncope is sometimes seen as a symptom of *hyperventilation.* It usually occurs while the patient is standing or sitting. It is prevented rather than precipitated by exercise. In this syndrome there is a disturbance of cerebral metabolism that is probably due to a combination of decreased cerebral blood flow secondary to orthostatic pooling of blood, and alkalosis.[6]

This type of syncope is readily diagnosed by reproduction of the symptoms during forced hyperventilation. All of the patients under discussion were subjected to this procedure and in no instance did syncope occur.

INABILITY OF THE HEART TO INCREASE THE CARDIAC OUTPUT NORMALLY IN RESPONSE TO EXERTION

It is possible that the syncope of these patients was the result of inability of the failing heart to increase its output normally during exertion. The opening up of a large arteriolar bed in the extremities as the result of exercise, without a corresponding increase in cardiac output, might precipitate a fall in arterial pressure with resulting cerebral ischemia and loss of consciousness. This is an interesting theoretical possibility, but there is no experimental evidence to support it. An attempt was made to test this hypothesis on two patients with aortic stenosis and attacks of syncope. After the patients became compensated, the vascular bed in the lower extremities was dilated by occluding the arterial inflow for fifteen minutes. There was no abnormal fall in arterial pressure when the tourniquets were released and blood entered the dilated vessels of the lower extremities. These experiments are not conclusive because cardiac function was much better than at the time when syncope was experienced.

CARDIAC ARRHYTHMIAS AND ADAMS-STOKES SYNCOPE

Paroxysmal cardiac arrhythmias, particularly paroxysmal auricular tachycardia and bradycardia, are at times accompanied by syncope. Paroxysmal auricular fibrillation and transient ventricular fibrillation are less commonly encountered. There is no evidence that any of these phenomena played a part in the syncope of the patients reported here.

In true Adams-Stokes syncope of nonreflex origin, attacks are caused either by a changing ventricular pacemaker in the presence of complete heart block, or by changing degrees of block with a shift in pacemaker from the sinoauricular to the auriculoventricular node. These attacks bear no apparent relation to exertion or to the position of the body.

It must be stressed that the mechanism of the syncope in the cases reported here is not understood. It may well be that several of the factors that have been discussed were involved. Inability of the heart to increase the cardiac output during exertion, and reflexes arising from engorged lungs and an ischemic myocardium would seem to be a reasonable working hypothesis. The question arises as to whether anginal pain is a necessary part of the syndrome described. As far as could be ascertained from the histories, these attacks of syncope were, in many respects, similar to those which occur with aortic stenosis. Many patients with aortic stenosis have attacks of syncope unaccompanied by angina. It would appear fair to assume that pain is not necessary for the production of syncope of the type discussed here, but that its presence may act as a precipitating factor.

Many more detailed observations are needed before a definite answer can be reached. All attempts to reproduce syncope in this group

met with failure. This can be explained, at least in part, by the unwillingness of the patients to exercise to the point of onset of symptoms, and the fact that their cardiac function was improved by therapy before the attempt to induce syncope was made. It remains for critical clinical, electrocardiographic, and perhaps electroencephalographic observations to be made by physicians who are able to see similar patients during attacks of unconsciousness.

SUMMARY

Cases of syncope associated with exertional dyspnea and angina pectoris have been presented. Several of the common types of heart disease are included in the group.

The patients described in remarkably the same manner the sequence of events leading to syncope. Syncope was always preceded by both exertional dyspnea and angina, and was prone to occur at times when congestive heart failure was most marked.

Physical examination failed to reveal anything other than the usual features of the underlying disease. With one exception, carotid sinus stimulation and hyperventilation produced no abnormal responses.

The various common types of cardiovascular syncope have been considered in connection with these patients. The cause of their syncope remains obscure, but it is suggested that exertion beyond the capacity of the cardiac output and reflexes arising from engorged lungs and an ischemic myocardium may be important factors.

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A SUGGESTION FOR IMPROVING THE STRUCTURE OF THE CARDIAC CORONARY CIRCULATORY SYSTEM WITHOUT SURGICAL INTERVENTION

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IT IS common knowledge among physicians in Puerto Rico that, among the poor classes in the rural mountainous sections of the island, anemia, due to an incidence of uncinariatic infestation of over 80 per cent, associated with a marked protein and vitamin deficiency in their diet, is so prevalent that it constitutes their most constant and significant medical characteristic.

After working for four years in these rural, mountainous regions, I have been able to observe in the inhabitants another medical characteristic, just as significant as their anemia, namely, extraordinary hearts.

There is nothing more astonishing and puzzling than to observe, for the first time, one of these very anemic peasants walking several miles up and down hills with extreme ease. One would never imagine that it could be possible for any heart to stand, with ease, the enormous double strain of severe anemia and such violent exercise. The stair test for cardiac functional efficiency used by cardiologists in cities appears insignificant by comparison. But one continues to see this so frequently, day after day, that it soon ceases to appear extraordinary. Otherwise, we could not explain why it has not been mentioned repeatedly in our local medical literature during the last half century.

Furthermore, among 1,565 white, poor patients, over 45 years of age, from these rural areas, observed in my general medical practice during these four years, there was not a single case of angina pectoris due to coronary disease, whereas, among 453 white, well-to-do patients, over 45 years of age, also observed in my practice during the same four years, there were five deaths from coronary disease and its complications.

Of course, angina pectoris does not necessarily mean coronary disease. It is only the clinical expression of acute myocardial anoxia. The heart muscle develops, on exertion, acute oxygen want, and this is manifested by precordial pain; this occurs whenever there is partial obstruction of the coronary arteries and its muscle fibers are unable to receive additional blood with the necessary additional oxygen (ischemic anoxia), or when its muscle fibers are unable to receive additional hemoglobin with the necessary additional oxygen (anemic

Received for publication Jan. 22, 1944.

anoxia).[1, 8, 10, 14, 15] Since not all of the hearts were examined when they had already developed a compensatory mechanism for anemia, as will be shown later, it is obvious that, among the large number of anemic patients studied, we have naturally seen some with precordial pain, with or without radiation, of short duration and induced by effort, but always in relation to anemic anoxia, and not to ischemic anoxia, and always disappearing spontaneously and completely as the anemia diminishes.

We must accept the fact that this represents a very limited series of cases, and that they have not been thoroughly analyzed. But the vital statistics of the Department of Health of Puerto Rico,[2] which are the only ones available, tend to corroborate the above to some extent. They show that the death rate from cardiac diseases is very much lower in the rural districts than in urban centers of the island. Nevertheless, these vital statistics do not help enough, because they include the mortality from all the diseases of the heart, whereas we refer exclusively to coronary disease. They also include the entire rural zone of the island, whereas we refer only to a special limited rural district where uncinariasis and anemia predominate enormously.

We are able to see, at least, that, in my limited personal experience, there appeared two clinically very significant and distinct groups of cases: One in which the patients rarely develop symptoms or die of coronary heart disease and its complications; the other, in which patients suffer and die of this condition at the usual rate.[18]

The two groups belong to the same race (white Puerto Ricans), are of approximately the same age (over 45 years), and live in the same geographical environment (1,500 to 2,500 ft. above sea level). They differ fundamentally in that the first group are very poor, live in the rural area, own very few latrines, walk barefooted, suffer an incidence of uncinariatic infestation of over 80 per cent, have a diet deficient in proteins and vitamins, and have the habit of nursing their children for a prolonged period of time. All these are factors that contribute to make anemia so prevalent in this group.

The other is a well-to-do group; they live in the urban zone, have toilets, wear shoes, seldom suffer from uncinariasis, have a more abundant and balanced diet, have lost the habit of prolonged nursing of their children, and, therefore, have no tendency to suffer from anemia with unusual frequency.

Anemia appears to be the prevailing and, possibly, the fundamental factor that, paradoxically, seems to exert a beneficial effect on the hearts of these country folk. Is it that anemia tends to prevent coronary sclerosis? Among these folk when they are over 45 years old, it is not rare to find evidence of sclerotic changes in the peripheral, retinal, cerebral, and renal arteries. If sclerotic changes are not uncommon in the rest of the arterial tree of these peasants after the age

of 45 years, it is to be expected that coronary sclerosis should also occur with some frequency among them. What actually happens is that when they suffer from coronary disease they do not tend to develop symptoms or to die from its complications with the usual frequency.

We see, then, that these country folk, among whom anemia is so prevalent, tend to possess extraordinary hearts:

1. Because of the unusual frequency with which they show extraordinary cardiac functional efficiency in the presence of severe anemia.
2. Because of their ability to tolerate silently (without symptoms) the coronary sclerosis that they may develop.
3. Because they so rarely die from the complications of coronary sclerosis.

Therefore, we came across clinical evidence suggesting most emphatically that, paradoxically, there may exist a so far unmentioned cardiologic phenomenon, namely, *anemia may exert a beneficial effect on the heart.*

In order to analyze this phenomenon without help, and without being able to transport to the mountains of Puerto Rico the necessary hospital facilities, with clinical, electrocardiographic, and radiologic laboratories, we had to apply an easy method that would give objective data as to how the individual heart reacts to anemia. It could not require any more instruments than a stethoscope and a hemoglobinometer, the only ones available.

Therefore, we started to look carefully into the so-called hemic murmurs, the physical sign to which little attention is paid in modern cardiology.[16] The accepted physiopathologic explanation is that these so-called hemic murmurs are not produced by any physical change in the blood that may be induced by anemia, but that they are due exclusively to weakness and dilatation of the cardiac muscle caused by the anoxemia induced by the anemia.[3] Naturally, when the cardiac muscle dilates, not only do the edges of the valves become separated, but the papillary muscles are also displaced, the chordae tendineae are unable to stretch sufficiently to permit perfect closure of the valves, and hemic murmurs are produced by functional valvular regurgitation. Like all regurgitative murmurs, these hemic murmurs are systolic if the dilatation occurs in the mitral or tricuspid valves, and diastolic if the dilatation affects the aortic or pulmonary openings.[3, 11, 16]

As a matter of fact, the dilatation occurs most frequently in the mitral or tricuspid openings, and, therefore, the hemic murmurs are almost always systolic. They lack any acoustic characteristic by which they could be identified. In the beginning, in cases of moderate anemia, they tend to be soft and localized. But when they progress with more severe anemia, they tend to become just as rough and loud, and to be transmitted just the same, as any other organic murmur.

The only thing that identifies these hemic murmurs is their fluctuations in direct proportion to the variations in severity of the anemia.

Therefore, because of their etiology, instead of hemic murmurs they should be called functional murmurs of myocardial anemic anoxia.

Then they assume their real clinical significance, for they are a very important objective sign of cardiac weakness induced by anemic anoxia, and, therefore, they may be used as an index of the ability of the heart to withstand anemia. In other words, a heart that develops hemic murmurs with a low-grade anemia must necessarily be weaker than another that tolerates this same degree of anemia without developing hemic murmurs. By the same token, a heart that is able to withstand severe anemic anoxia without developing hemic murmurs must be an extraordinarily good one.

We decided, therefore, to utilize this index of hemic murmurs in an attempt to obtain some objective evidence that would add or subtract weight to our clinical observations. Thus, we proceeded carefully to correlate the presence or absence of hemic murmurs with the hemoglobin level in poor patients over 2 years of age, with apparent anemia, from the mountainous rural districts.

In order to eliminate organic regurgitative murmurs, we excluded from the series all anemic patients with serologic or clinical evidence of syphilis and with active, or with a past medical history suggestive of, rheumatic infection.

Since the heart may be weakened and dilated not only because of anemic anoxia, but also, and mainly, by toxic infectious states, hyper- or hypothyroidism, and in beriberi, we also excluded all anemic patients with clinical evidence of the above mentioned conditions.

To eliminate as far as possible other nonanemic functional murmurs, we examined all patients in the erect posture.

To eliminate cardiopulmonary murmurs, we always made sure that the hemic murmurs persisted during apneic periods. The Tallqvist scale was used uniformly. All of the hemoglobin estimations and the auscultation were done personally in every case, so that any error would be constant and would not affect considerably the comparative value of the figures obtained in the series.

Our series, thus obtained, consists of 833 patients with apparent anemia, of which only 187, or 22.4 per cent, had hemic murmurs. In other words, approximately only one of every five anemic peasants studied had hemic murmurs, an incidence much lower than would be generally expected. We have not been able to find in the literature available in the library of the School of Tropical Medicine of Puerto Rico any similar analysis of the incidence of hemic murmurs, but only general impressions to the effect that they occur with such great frequency in anemic states that they do not deserve any commentary.[16]

The preceding discussion tends to corroborate objectively our clinical observation that the hearts of the peasants from the mountains of Puerto Rico, among whom uncinariasis and anemia are so prevalent, tend to be extraordinary, in most of the cases, because of their ability to compensate and preserve functional efficiency in the presence of apparent anemia without weakening, dilating, or developing hemic murmurs.

Table I shows the distribution of the cases and of patients with hemic murmurs at different levels of anemia.

TABLE I

GRADE OF ANEMIA	HB. (%)	TOTAL NUMBER OF CASES	TOTAL NUMBER OF PATIENTS WITH HEMIC MURMURS	INCIDENCE OF HEMIC MURMURS (%)
Moderate	60	320	60	18.4
Severe	50	422	82	19.2
Very severe	40	74	28	39.2
Extreme	30	17	17	100.0

It shows the direct relation between the increase in severity of the anemia and the increase in frequency with which hemic murmurs occur. Naturally, the more severe the anemic anoxia, the more difficult it is for the heart to compensate, and the more frequent the occurrence of the hemic murmurs. It also shows that the heart is able to compensate only to a certain extent, and, whenever the anemic anoxia exceeds this limit, 100 per cent of the hearts grow weak, dilate, and develop hemic murmurs.

Table II shows the distribution of cases and the incidence of hemic murmurs among patients under 30 years of age and those 30 years of age and over.

TABLE II

AGE	TOTAL NUMBER EXAMINED	TOTAL NUMBER WITH HEMIC MURMURS	PERCENTAGE WITH HEMIC MURMURS
Under 30 years	639	158	24.7
30 years and over	194	29	14.9
Total	833	187	22.4

The percentage of patients with hemic murmurs in the younger group, who would be expected to have better hearts, is distinctly higher than in the older group, who would be expected to have weaker hearts. This suggests that these peasants do not inherit, or are not born with, unusual hearts which are capable of tolerating anemia exceptionally well, but that their hearts probably develop a special compensatory mechanism for anemia during their lifetime. The older the person, the more the opportunities for acquiring uncinariasis and anemia, and the more frequently the compensatory mechanism for

anemia will tend to develop, with a smaller incidence of hemic murmurs. It also shows that older hearts, after developing some sort of a special compensatory mechanism for anemia, are more capable of withstanding anemic anoxia than supposedly stronger, younger hearts that have not yet developed this special compensatory mechanism.

TABLE III

AGE	60% HB.			50% HB.			40% HB.			30% HB.		
	TOTAL CASES	NUMBER POSITIVE WITH HEMIC MURUMRS	PERCENTAGE POSITIVE WITH HEMIC MURMURS	TOTAL CASES	NUMBER POSITIVE WITH HEMIC MURMURS	PERCENTAGE POSITIVE WITH HEMIC MURMURS	TOTAL CASES	NUMBER POSITIVE WITH HEMIC MURUMRS	PERCENTAGE POSITIVE WITH HEMIC MURMURS	TOTAL CASES	NUMBER POSITIVE WITH HEMIC MURUMRS	PERCENTAGE POSITIVE WITH HEMIC MURMURS
Less than 30 years	244	49	20.0	320	68	21.0	58	24	41.3	17	17	100
30 years and over	76	11	14.4	102	14	13.7	16	4	25.0	--	--	--
Total	320	60	18.8	422	82	19.4	74	28	37.8	17	17	100

TABLE IV

AGE (YEARS)	60% HB.			50% HB.			40% HB.			30% HB.		
	TOTAL CASES	TOTAL CASES WITH HEMIC MURMURS	INCIDENCE OF HEMIC MURMURS (%)	TOTAL CASES	TOTAL CASES WITH HEMIC MURMURS	INCIDENCE OF HEMIC MURMURS (%)	TOTAL CASES	TOTAL CASES WITH HEMIC MURMURS	INCIDENCE OF HEMIC MURMURS (%)	TOTAL CASES	TOTAL CASES WITH HEMIC MURMURS	INCIDENCE OF HEMIC MURMURS
10 to 19	146	28	19.1	182	46	25.2	21	11	52.3	4	4	100
40 to 79	35	1	2.8	75	6	8.0	10	3	30.0	-	-	--

Table III shows the incidence of hemic murmurs in relation to age and severity of the anemia. It shows that the incidence of hemic murmurs is maintained distinctly higher in the younger than in the older group at all hemoglobin levels. This tends to corroborate and add weight to the deductions derived from Table II.

Table IV shows the incidence of hemic murmurs at different hemoglobin levels in two groups of patients who were more distinctly and widely separated in age. Again we see even more clearly the distinct tendency for hemic murmurs to occur more frequently among the younger patients and that this tendency is maintained constantly at the different hemoglobin levels.

Table V, from which all previous ones were constructed, shows the distribution of cases according to age, grade of anemia, and presence or absence of hemic murmurs.

TABLE V

AGE (YEARS)	HEMIC MURMURS	HB. 30%	HB. 40%	HB. 50%	HB. 60%	TOTAL
Less than 10	+	11	8	8	4	31
	−	0	17	59	28	104
	Total	11	25	67	32	135
10 to 19	+	4	11	46	28	89
	−	0	10	136	118	264
	Total	4	21	182	146	353
20 to 29	+	2	5	14	17	38
	−	0	7	57	49	113
	Total	2	12	71	66	151
30 to 39	+	0	1	8	10	19
	−	0	5	17	29	51
	Total	0	6	25	39	70
40 to 49	+	0	1	3	1	5
	−	0	3	30	15	48
	Total	0	4	33	16	53
50 to 59	+	0	1	2	0	3
	−	0	0	27	10	37
	Total	0	1	29	10	40
60 to 69	+	0	1	0	0	1
	−	0	4	8	6	18
	Total	0	5	8	6	19
70 to 79	+	0	0	1	0	1
	−	0	0	4	3	7
	Total	0	0	5	3	8
80 and over	+	0	0	0	0	0
	−	0	0	2	2	4
	Total	0	0	2	2	4
Total	+	17	28	82	60	187
	−	0	46	340	260	646
	Total	17	74	422	320	833

From Table V we can pick out different groups that are still more suggestive because of the marked contrast among them, for instance:

Group I.—This group includes 32 youths under 20 years of age, all with only moderate anemia (60 per cent Hb.), and yet all had hemic murmurs.

Group II.—This group includes 27 youths of approximately the same age, under 20 years, but with very severe anemia (40 per cent Hb.), and yet none of them had hemic murmurs.

Group III.—This group includes 41 elderly persons, all over 50 years old, all with severe anemia (50 per cent Hb.), and yet none had hemic murmurs.

Group IV.—Includes 11 persons over 70 years of age, with moderate to severe anemia (60 per cent to 50 per cent Hb.), and yet none had hemic murmurs.

Hence, either the accepted physiopathologic explanation of the so-called "hemic murmurs" is wrong, and there is some other factor in their pathogenesis besides weakening and dilation of the heart induced by myocardial anoxia, or we must admit that the heart is capable of

developing some sort of special compensatory mechanism whenever obliged to do so by anemia. If we accept the latter view we must also accept, as within the realm of reasonable possibilities, the following deductions and generalizations derived from the different tables:

1. The normal heart is so sensitive to anemic anoxia that even strong, youthful hearts are weakened, become dilated, and develop hemic murmurs in the presence of even moderate anemia (60 per cent Hb.).

2. That anemia compels the heart to develop a special compensatory mechanism that allows it to stand the anoxia induced by the anemia up to a certain limit, without weakening, dilating, or developing hemic murmurs.

3. That whenever a heart develops this special mechanism to its maximum, it is capable of tolerating even the anoxia of very severe anemia (40 per cent Hb.) without weakening, dilating, or developing hemic murmurs.

4. That this special compensatory mechanism tends to have a limit, and when the anemia becomes extreme (30 per cent Hb.), and the anemic anoxia surpasses it, all the hearts are weakened, become dilated, and develop hemic murmurs.

5. That, whenever anemia prevails in a group of patients, this special compensatory mechanism develops among them with more frequency, and, hence, with less frequency will hemic murmurs appear among them during subsequent anemias.

6. That youthfulness does not necessarily imply a better heart. The hearts of persons over 50 years of age, after having developed this special compensatory mechanism, are more efficient in withstanding anemic anoxia than the youthful hearts of persons less than 30 years of age that have not as yet developed this special compensatory mechanism.

7. That, after this special compensatory mechanism is developed, it continues to function throughout life, and allows the heart to withstand severe subsequent anemias that may develop in old age (over 50 years), and even in senility (over 70 years), without weakening, dilating, or developing hemic murmurs.

8. That, by inference, (a) since the ability of the heart to tolerate anoxia of exercise induced by increased metabolic rate, with its enormous increase in oxygen demand (it is calculated that, in spite of its small size compared with that of the rest of the body, the heart burns during exercise as much oxygen as the rest of the body during repose[4]), is the fundamental basis of all tests for cardiac reserve; (b) since anoxia induced by exercise is even being substituted by anoxia induced by reduction in oxygen tension of the inspired air in special electrocardiographic tests of cardiac efficiency;[5-7, 12, 13] and (c) since anoxia is the fundamental factor, and it makes no difference whether myocardial anoxia is induced by anemia or by exercise; therefore, a heart compelled to develop this special compensatory mechanism for anemic

anoxia, if it continues to function throughout life, would be just as well prepared to withstand, with the same ease, the anoxia of exercise as the anoxia of future anemias; and, hence, a previous, temporary anemia may be capable of permanently transforming an ordinary, normal heart into a more efficient one with greater cardiac reserve and more functional capacity.

9. That, by inference, since, physiopathologically, it also makes no difference whether anoxia is of anemic or ischemic (obstructive) origin, the same special compensatory mechanism will enable the heart to withstand anemic as well as ischemic anoxia; and, therefore, after this special compensatory mechanism is fully developed, the heart would be just as well prepared to endure, with the same impunity, subsequent anemias that may develop in old age, as well as the coronary sclerotic changes of late middle, and old, age.

Thus we may say that the new cardiologic phenomenon, mentioned in the beginning, whose presence was suggested by clinical observations, probably exists, and does not necessarily constitute a great paradox, namely, *moderate temporary anemia may exert a beneficial effect on the heart by compelling it to develop some special compensatory mechanism that continues to function throughout life, and allows the heart to tolerate with impunity, up to a certain limit, the myocardial anoxia that develops from subsequent anemias, as well as from exertion or coronary sclerosis.*

We have to try now to find a reasonable physioanatomic explanation of the nature of this special compensatory mechanism and the manner in which it is developed.

It is known, of course, that compensation for anemia is carried out by the organism as a whole; in part, by forcing hemoglobin to liberate a greater amount of its load of oxygen to the tissues; in part, by forcing the tissues to utilize oxygen with greater efficiency; but mainly, by forcing the heart to pump an increased minute-volume of blood to the tissues.[26, 27]

Scaramucci, an Italian of the seventeenth century, first called attention to the fact that the flow of blood in the coronary arteries occurs mainly during diastole, instead of systole, as in the rest of the arterial tree, because the coronary arteries are compressed during systole by the contraction of the cardiac muscle. We also know that tachycardia takes place mainly at the expense of the diastolic period, with relatively little reduction in the systolic period. Tachycardia, therefore, results in a greater increase in transportation of oxygen throughout the systemic arterial system than in the coronary arteries.

In order that the heart may be able to compensate for its own anemic anoxia, with the added burden of the increased work that is imposed upon it to compensate for the anemic anoxia of the entire organism, and without being able to utilize as favorably its own increased rate for its own increased oxygenation, it must necessarily provide itself

with an added means of augmenting the minute-volume flow of blood that reaches its muscle fibers.

According to Wearn,[22] the adult human heart has what can be called a perfect proportion of one capillary per muscle fiber. This represents an average of approximately 3,342 capillaries per square millimeter of cardiac muscle, and about twice the number of capillaries per muscle fiber in skeletal muscles. Obviously, any compensatory increase in blood supply to the heart muscle should be looked for in the coronary arterial system that supplies this prodigious capillary bed.

It is no longer considered that the coronary circulatory system is an *end-artery* system. On page 549 of *Gray's Anatomy,* twenty-fourth edition, it is stated that there is an extensive anastomosis between the small branches of the coronary arteries in the substance of the heart. Besides these extensive intercoronary anastomoses, the coronary arteries communicate with extracardiac arteries and also with the ventricular cavities through arterioluminal and arteriosinusoidal vessels.[4, 22]

According to Goldsmith and Butler,[21] among the higher vertebrates the thebesian or intertrabecular circulation is the primitive one and the one that functions in the fetus long before the coronary system is developed. Some of these thebesian vessels become permanently incorporated in the coronary arterial system, and some remain as permanent arterial communications between the coronary arteries and the internal cavities of the heart. The thebesian veins drain the capillary spaces directly into the internal cavities of the heart. By retrograde flow these veins may also contribute to the nutrition of the myocardium.

We see, therefore, that in the anatomic sense the coronary arteries are not terminal arteries. Nevertheless, all this vast net of collateral vessels exist only as a potential, nonfunctioning, impermeable anastomosis. Hence, in the physiologic sense the coronary artery system continues to be an end-artery system, and myocardial infarction occurs when one of its branches is suddenly obliterated.[23]

Blumgart, Schlesinger, and Davis[19] have shown that in the normal heart there are no intercoronary anastomoses larger than 40 micra in diameter, but that anastomotic vessels less than 40 micra in diameter are very numerous, and that they can be easily demonstrated when injections are performed with watery fluid of low viscosity. In other words, these numerous intercoronary anastomotic vessels which are found in normal hearts are too small to permit the flow of a liquid with the viscosity of normal blood, and, therefore, are of no functional significance.

On the contrary, in hearts which were the seat of chronic coronary obstruction these authors were able to demonstrate a marked increase in the size of these intercoronary anastomotic vessels, reaching up to 200 micra in diameter, and, hence, with full functional capacity because they could be injected with a lead-agar mass. Furthermore, these authors proved by comparative clinicopathologic studies that, if

occlusion of a coronary artery takes place gradually, throughout months or years, with a concomitant efficient development of these intercoronary anastomotic vessels, (1) the supply to the corresponding portion of myocardium remains adequate for the ordinary activities of life; (2) there are no demonstrable physical signs or symptoms during the lifetime of the patient; and (3) no scar can be demonstrated in the myocardium at autopsy. Therefore, the extraordinary compensatory significance of collateral circulation through enlarged intercoronary anastomotic vessels in myocardial areas subjected to chronic ischemia is emphasized.

Now these enlarged, fully functional, intercoronary anastomotic vessels, with full compensatory capacity, have been demonstrated both at autopsy and experimentally in dogs, always and exclusively associated with chronic obstruction in the coronary arteries and their branches.[19, 20, 24] Therefore, it has been generally believed that the increase in pressure induced by chronic obstruction in the coronary circuit is the only factor responsible, and the only one able to force dilatation and to initiate blood flow, with subsequent development of these small, previously impervious and nonfunctioning intercoronary anastomotic vessels.

Anemia causes no increase in pressure in the coronary circuit, but, since anemia reduces considerably the viscosity of the blood and through anoxemia induces very marked vasodilatation, and since in circulatory dynamics the sum of these two factors, vasodilatation plus reduced viscosity, is always capable of compensating for a lack of a moderate increase in pressure, we may conclude tentatively:

1. That it is not necessary, as is generally believed, for the coronary arteries to become chronically obstructed in order to force, through an increase in pressure, these collateral intercommunicating vessels to become dilated and assume efficient function.

2. That anemia by itself, with the ordinary pressure in the coronary circuit, but helped by the vasodilatation and reduction of blood viscosity that it produces, may be equally capable of starting blood flow, with the subsequent development of the collateral anastomotic vessels of the coronary arterial system.

3. That, with chronic coronary obstruction, the increased pressure induced in the coronary circuit can only exert its force and produce active dilatation in the intercoronary communicating branches; the other, very important arterioluminal and arteriosinusoidal anastomotic vessels could not be affected directly because the flow of blood in these vessels is in an opposite direction, that is, from the ventricular cavities toward the capillary bed of the myocardium.

4. That, with anemia, on the contrary, the passive, spontaneous vasodilation induced by anemic anoxia, plus the reduced viscosity of the blood, would exert an opening effect in the entire system of previously impervious anastomotic vessels.

5. That this probable ability of anemia to establish efficient function in the whole, vast, previously impervious collateral anastomotic circulatory system of the heart, including the extracardiac, arterioluminal, and arteriosinusoidal, besides the intercoronary vessels, may account for the special compensatory mechanism that the heart is capable of developing when compelled to do so by anemic anoxia.

Furthermore, how jealously the human organism guards itself against anoxemia and the numerous defences that are capable of being called into action as soon as oxygen hunger develops are well known. Since in the anoxemia of high altitudes (over 5,000 ft.) the organism is capable of compelling the hematopoietic system to produce a compensatory hyperglobulia and hyperhemoglobinemia; since, as shown experimentally in dogs by Whipple,[34] when anemia is superimposed on a severe dietary protein restriction, the organism is capable of altering protein metabolism in order to utilize the little amount of protein ingested, first and preferably, in the manufacture of hemoglobin, before any serum albumin or serum globulin is formed, with complete disregard for the edema which results from reduced osmotic pressure in the blood; since, in anemic anoxia, as mentioned before, the organism is capable of altering the oxidative processes in order to compel the hemoglobin to liberate a larger proportion of its oxygen load to the tissues and to compel the tissues to utilize oxygen more efficiently; and since, even in avascular tissues like the cornea, when its oxidative system is impaired, compensatory vascularization takes place to overcome local asphyxia, it should also be possible and is to be expected that, in the presence of chronic myocardial anemic anoxia, the organism may simply call into rapid growth and full function its vast reserve of undeveloped collateral anastomotic coronary vessels, in order to provide the myocardium with a compensatory increase in blood supply.

This is probable, not only from a physiologic point of view, but anatomically, it is also feasible, for, according to Goldsmith and Butler,[21] the coronary arterial system probably develops by budding instead of by the coalescence of intercellular spaces; and, according to Wearn,[22] there is a *constant morphologic alteration in the coronary circulation of the normal human heart,* with progressive improvement in the capillary, muscle-fiber ratio from one capillary per five muscle fibers at birth to one capillary for each muscle fiber at full maturity (30 years of age), after which this ratio remains constant throughout life.*

Hence we venture to propose the following tentative theory:

The existence of a moderately severe but tolerable anemia for a sufficient length of time is capable of exerting a distinctly beneficial effect

*Wearn states that this increased capillary, muscle-fiber ratio does not tend to improve the nutrition of the adult cardiac muscle fiber because the adult myocardial fiber is approximately 5 times as large as those of the newborn. Thus, the higher incidence of hemic murmurs among anemic persons less than 30 years of age, as compared to those over 30 years old, as shown in Tables II and III, cannot be explained by this improved capillary, muscle-fiber ratio of adults.

on the normal human heart by permanently changing the imperfect, susceptible, and dangerous coronary circulatory system (of the end-artery type, in the physiologic sense) into a much more efficient, well-guarded, nonsusceptible, and nondangerous one, with total development and full function in all its vast reserve of intercommunicating vessels.

That nature, a priori, should not deny man a physiologic method of developing the facultative function of this vast net of collateral anastomotic vessels in order to perfect the cardiac coronary arterial system and bring it up to par with the prodigious capillary bed with which the heart is provided beforehand, should follow from the fact that there is provision for a period of physiologic anemia in infancy, during all the time of exclusive lactation beyond six months, because of the deficiency of iron in milk, and because the child can accumulate only about a six months' reserve of iron during fetal life.

And while modern pediatricians pride themselves for their efficiency in eliminating this physiologic anemia of infancy with their ever advancing methods of supplementary feedings, modern surgeons are exerting themselves in trying to develop and to perfect even the most heroic surgical methods[28-32] that would give the desperately needed additional blood supply to the hearts of an ever increasing number of middle-aged patients, especially among the intellectual classes.

According to Marvin,[33] among these surgical methods, cardio-omentopexy and the implantation of the pectoralis minor on the heart have proved so far of very limited value, and he believes that they will have to be abandoned, but Brauer's artificial adhesive mediastinopericarditis has helped a few patients, and cannot be totally discarded.

May the day come soon when we can identify beyond doubt, and can feel fully justified in cooperating with, nature's methods, and can discard all heroic surgical procedures, not because of their imperfections, but because they are not necessary.

White, at the end of his book on heart disease,[3] has added an appendix of cardiological questions that have not been answered. Number 105, on page 885, reads as follows: *"Why is angina pectoris so rare in the Negro race"?* This is so, in spite of the fact that syphilis is more prevalent among Negroes than among whites in America. Among these American Negroes there are also much poverty, avitaminosis, and protein malnutrition, besides uncinariasis (in the South) and the habit of prolonged breast feeding of their children. Anemia in their youth, therefore, may have improved their coronary circulatory system to such an extent that, when they reach late middle age, they are capable, as are the peasants (whites) in Puerto Rico, of enduring aortitis and coronary artery disease without developing cardiac anoxia, and, hence, without angina pectoris.

Naturally, our only intention has been to try to develop and to propose this tentative theory, and not to commit the error of assuming that it is already established and could have any application as yet.

We do not call this a preliminary report only because we are afraid that, in the mountains of Puerto Rico, without facilities, we shall never be able to proceed any further, but we ardently hope that someone better equipped will be sufficiently stimulated to carry on and see whether it is possible to demonstrate, experimentally in dogs kept sufficiently anemic for a sufficient length of time, and in autopsies in cases in which there was a definite history of anemia in youth, the presence of a structural improvement in the coronary circulatory system.

Substantiation of this theory, and not its enunciation, would represent a truly valuable contribution to humanity, for only its absolute verification would make its application permissible, and only then would a promising new road be laid open to the prophylaxis of coronary heart disease, and, perhaps, even to the addition of a number of useful years to the average life span of man.

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CARDIAC HYPERTROPHY OF UNKNOWN CAUSE

A Study of the Clinical and Pathologic Features in Ten Adults

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THERE is a group of cases, observed in youth and in adult life, which is characterized chiefly by cardiac hypertrophy of obscure etiology. Most of these patients suffer, over varying periods of time, from recurring attacks of cardiac insufficiency of increasing severity; some die suddenly. Excluding the ten cases forming the basis of this study, reports of only fourteen examples of this condition were found in which a careful search at autopsy failed to reveal lesions characteristic of the familiar causes of heart disease. The first was recorded by Josserand and Gallavardin,[1] in 1901 (their Case 3). Laubry and Walser[2] reported a second in 1925, and applied the descriptive term "myocardie." Walser,[3] in his monograph, added a third. Cabot's messenger boy[4] first had symptoms of heart failure one year before his death at the age of 16 years. In 1933, Levy and Rousselot[5] reported three cases in young adults, one of which was subsequently discarded because of the possibility that the cardiac lesions were due to abnormal glycogen storage (von Gierke's disease). Whittle's Cambridge student,[6] referred to by these authors, should likewise be omitted, for post-mortem examination revealed a hypoplastic aorta and an enlarged thymus gland.

In 1937, Levy and Von Glahn,[7] in abstract form, recorded observations on ten cases, including two of those previously reported by Levy and Rousselot. It became apparent that, although the condition was uncommon, it was not as rare as had been believed, and that it presented a distinct pattern, both clinically and at autopsy. Subsequently, von Bonstorff[8] described eight cases from the Thorndike Memorial Laboratory of the Boston City Hospital, and Reisinger and Blumenthal,[9] two cases from the Veterans' Administration in Washington. Three additional cases included by the latter authors are not considered acceptable because of probable syphilitic lesions in the aorta. The tobacconist, whose story was given by Kjaergaard[10] and cited by von Bonstorff, must be omitted because of the incomplete autopsy notes and the statement that, microscopically, fatty degeneration and slight inflammatory lesions were found in the heart. Eleven cases are mentioned as falling into the category of "hypertrophy of uncertain

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Received for publication Feb. 21, 1944.

etiology'' by Kaplan, Clark, and de la Chapelle,[11] and another is referred to by Dexter and Farnsworth,[12] but individual histories and autopsy protocols are lacking, so that they cannot properly be included in the series. Deficiency of vitamin B was considered responsible for the cardiac disturbances in Dock's cases.[13] Those of Smith and Furth[14] were characterized by marked and widespread endocardial fibrosis. There is a curious form of degeneration of the myocardium associated with pregnancy and the puerperium, which results in congestive heart failure.[15, 16] It presents the common factor of unknown cause, but does not otherwise resemble the disorder with which we are concerned.

Although the main features of the ten cases to be described were given in our preliminary paper,[7] it has seemed desirable to document them by clinical histories and autopsy notes, as well as by suitable illustrations. A collection of such studies eventually may give a clue to the etiology.

ABSTRACTS OF CLINICAL RECORDS AND AUTOPSY PROTOCOLS

CASE 1.*—Unit No. 81203. G. T., a Negro man, married, aged 31 years, was admitted to the surgical service on May 10, 1929. He had been a rock-driller for ten years. He complained of a painful swelling in the right groin which had been present for three weeks. There were no cardiac symptoms. He gave an indefinite history of ''rheumatism'' in the right hip fourteen years previously, which never recurred. He had gonorrhea at the age of 14 years. He never had a serious illness. He smoked two packages of cigarettes a day and rarely took alcohol.

Examination showed that the heart was enlarged to the left. The sounds were of poor quality, and a soft systolic murmur was heard at the apex. The blood pressure was 100/60. The Wassermann reaction of the blood was negative. The leucocyte count was 9,700, with 70 per cent polymorphonuclears. The urine contained neither albumin nor sugar. Roentgenograms of the chest showed no areas suggesting tuberculous infiltration, but the heart shadow was enormously enlarged, particularly to the left.

A mass of infected lymph nodes in the right inguinal region was incised and drained. Microscopic examination of a bit of tissue removed at operation showed no tubercles and no caseation necrosis. A definite diagnosis of tuberculous adenitis could not be made. The patient was discharged on May 19, with a granulating wound.

Two weeks later he entered the city tuberculosis sanatorium at Seaview, where he remained two and one-half months. While there, an inguinal hernia was repaired. He gained 10 pounds and was told that he did not have pulmonary tuberculosis. The night before he left this institution he had his first attack of dyspnea, and was unable to sleep because of difficulty in breathing. In spite of this fact, he soon returned to his job, but after working for one day he again had a sudden attack of shortness of breath, and was obliged to stop. Dyspnea continued, and palpitation and precordial pain appeared. On September

*Cases 1 and 7 were described in a previous paper (Levy and Rousselot,[5] Cases 1 and 3). In order to bring all of the material together, they are reported again.

2 (three and one-half months after leaving the hospital and three days after resuming work), he was readmitted to a ward of the Presbyterian Hospital.

On admission, he was quite short of breath and looked ill. The temperature was 101.2° F. There were coarse râles scattered throughout both lungs. The heart was greatly enlarged to the left. The rate was 104, the rhythm was regular, and the sounds were of fair quality. There was a soft systolic murmur at the apex. The blood pressure was 98/72; it rose on the following day to 106/86. There was slight clubbing of the fingers. The liver and spleen were not enlarged. The erythrocyte count was 4,260,000; the hemoglobin, 80 per cent; and the leucocytes, 7,800, with 64 per cent polymorphonuclears. The Wassermann reaction of the blood was again negative. No tubercle bacilli were found in the sputum at any time. The blood urea was 26 mg. per 100 cubic centimeters. Numerous blood cultures were negative. Roentgenograms of the chest showed patchy areas of density in the lower third of the right lung, suggesting pneumonic consolidation. The heart shadow was enormously enlarged. The electrocardiogram showed sinus tachycardia, with a rate of 120, and well-marked left axis deviation. The P-R interval was 0.15 second. The T wave was inverted in Leads I and II, and upright in Lead III.

There was continuous elevation of temperature, with fluctuations from 98 to 104.8° F. There was also sustained tachycardia; the rate usually ranged between 90 and 110. On November 14, auricular fibrillation, with a rate of 72, was observed. Four days later, sinus rhythm reappeared. The leucocytes were never greatly increased; the highest count recorded was 12,000, with 85 per cent polymorphonuclears. There was no anemia.

On September 12 (ten days after admission) he complained of sudden blindness in the left eye, and it was apparent that an embolus had lodged in the central artery of the retina. Subsequently, expectoration of blood and pain in the left lumbar region suggested infarction of the lungs and left kidney. The blood pressure remained low—100 to 108 mm. Hg, systolic; 64 to 88, diastolic. Cardiac insufficiency gradually increased and a cardiac psychosis developed. He died on December 30 (four months after admission), of advanced myocardial insufficiency.

*Clinical Diagnosis.**—Cardiac hypertrophy; cardiac thrombosis; chronic myocarditis; infarcts of lung and spleen; embolism of central artery of retina.

Autopsy No. 10368.—Heart: Weight, 640 grams. There were small deposits of fibrin on the pericardial surface of both auricles and each ventricle; these were most marked at the apex. The auricles were of normal size, the ventricles were dilated, especially the right ventricle in the region of the conus. Both ventricular walls were hypertrophied; the right measured 1.1 cm., the left, 2.5 cm., in thickness. The papillary muscles of the right ventricle were somewhat hypertrophied. At the apex of the right ventricle there were numerous small thrombi, and similar thrombi were present between the columnae carneae at the apex of the left ventricle. Beneath these thrombi in the left ventricle the myocardium was greatly thinned out, and fine fibrous strands extended from the endocardium into the muscle. The endocardium of the septal portions and anterior wall of the right ventricle was thick-

*The clinical diagnoses are given exactly as they appeared on the charts. The terminology varies with the current fashion, depending upon the date of observation.

ened to form narrow white streaks. The endocardium of the left ventricle was thickened. The tricuspid valve had four cusps; the other valves were normal except for slight thickening of the margin of the mitral cusps.

The coronary arteries were normal except for slight intimal thickening of the left branch.

Aorta: Normal.

Histologic Examination.—The myocardium was hypertrophied; the nuclei were irregular in shape. Occasionally, small hemorrhages separated the muscle fibers. On the endocardial surface there were completely organized and more recently formed thrombi. There was no acute inflammatory reaction. Gram and Levaditi stains did not reveal any organisms.

Final Note.—The central lesion at autopsy was an enlarged heart, with parietal thrombi but without any significant valvular or myocardial lesions. The changes in the other organs were those associated with embolism and infarction from mural thrombi and with cardiac insufficiency. It view of the patient's history of ten years of rock-drilling, one might anticipate silicotic changes. The cough and roentgenologic observations were in accord with this possibility, but sections of the lung offered no support for this diagnosis. The enlarged lymph nodes in the groin, because of which the patient originally entered the hospital, contained structures which resembled tubercles, but the etiology could not be proved. The cause of the cardiac dilatation and mural thrombosis remained undiscovered. There were no clear-cut inflammatory changes other than those associated with the organizing thrombi.

Anatomic Diagnosis.—Cardiac hypertrophy and dilatation; mural thrombi in ventricles; infarcts of lung, right, and both kidneys; chronic passive congestion of viscera; hydrothorax, bilateral; hydropericardium; ascites; edema of extremities; tuberculosis of inguinal lymph nodes; chronic prostatitis; congenital malformation of heart (patent foramen ovale and quadricuspid tricuspid valve).

CASE 2.—Unit No. 52367. E. H., a white woman, aged 48 years, a housewife, was admitted to the hospital on Dec. 23, 1921, complaining of shortness of breath and pain in the lower abdomen. Several years previously hysterectomy was performed because of bleeding fibroids. For eight months she was short of breath and distended. There was pain in both arms and in both lower abdominal quadrants. The ankles and legs were swollen for two months.

Examination showed dyspnea, orthopnea, and cyanosis. The veins of the neck were distended. The temperature was 100.4° F. There were signs of congestion in both lungs, with fluid in the right pleural sac. The heart was greatly enlarged to the left. The cardiac rhythm was totally irregular; the rate ranged from 80 to 120. The blood pressure was 130/80. The liver was enlarged. There was marked edema of the lower extremities.

During the night after admission she became weaker, the pulse grew feebler, and she died of myocardial insufficiency.

Clinical Diagnosis.—Chronic myocarditis; cardiac hypertrophy and dilatation; cardiac insufficiency; auricular fibrillation.

Autopsy No. 9185.—Heart: Weight, 550 grams. There was an adhesion between the posterior surface of both ventricles and the parietal pericardium; this adhesion covered an area of about 4 cm., with its

upper margin at the auriculoventricular grooves. The apex of the heart was blunt and rounded, and was formed by both ventricles. All of the cavities were dilated, especially that of the right ventricle. The various valves were normal. At the apex of the left ventricle there was a large, dark-red thrombus with a corrugated surface. The endocardium of the left ventricle was grey and more opaque than normal, but in the other chambers it was unaltered. The myocardium was pale red, flabby, and without any obvious increase of connective tissue. The right ventricle was 6 mm. in thickness, the left, 14 millimeters. Only a few areas of early sclerosis were found in the coronary arteries.

Aorta. This was moderately sclerotic.

Histologic Examination.—Heart: The myocardium of the left ventricle was moderately hypertrophied; the nuclei were larger than normal and were hyperchromatic. There was no necrosis and no scarring. The capillaries were engorged (Fig. 1). The arterioles were normal.

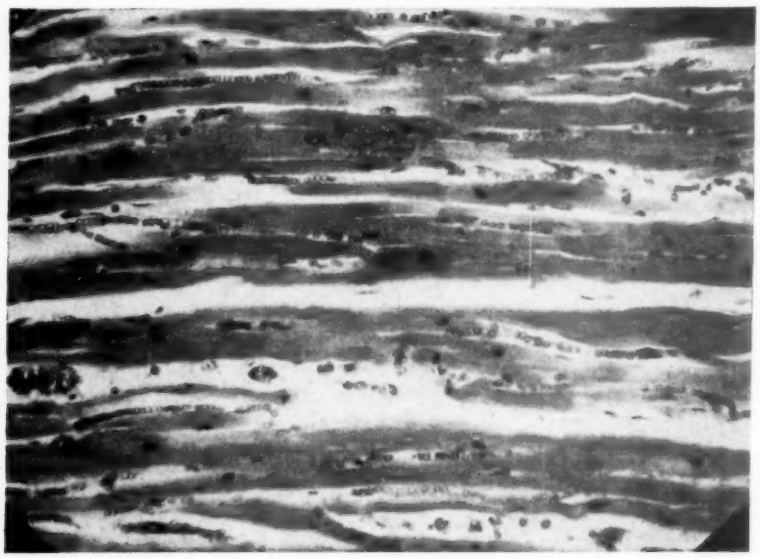


Fig. 1.—Case 2. Hypertrophy of myocardium.

Final Note.—The autopsy offered no satisfactory explanation of the cardiac derangement. There were no changes in the myocardium or peripheral arteries sufficient to explain the cardiac incompetency.

Anatomic Diagnosis.—Cardiac hypertrophy; pericardial adhesion; thrombus of left ventricle; infarcts in lung, right, and kidney, left; chronic passive congestion of viscera; hydrothorax, right; ascites; adenoma of thyroid.

CASE 3.—Unit No. 356074. D. E., a white man, aged 56 years, married, an unemployed salesman, was admitted to the hospital on Oct. 7, 1932, complaining of swelling of the ankles and asthma. He had pneumonia twelve years previously, and this was followed by attacks of asthma, which persisted. There was almost continuous wheezing; dyspnea was worse on exertion. Skin tests were negative for allergic sensitivity. The asthma was worse in winter than in summer. Eating beef and exposure to dog's hair aggravated the condition.

Three months earlier his business failed and he was forced to give up his motor car. This necessitated more walking, and he climbed many flights of stairs in the effort to make a living. Edema of the ankles steadily increased. He was given digitalis without apparent benefit. For twenty-four hours before admission, his wife noted cyanosis and an increase in the heart rate to 120.

Examination showed the man to be acutely ill, cyanotic, dyspneic, and orthopneic. There were râles and dullness at the bases of both lungs. The heart was greatly enlarged. The rate was 100; the rhythm was regular save for occasional premature beats. The sounds were feeble; a blowing systolic murmur was heard at the apex. The blood pressure was 150/95. The liver was enlarged. There was marked edema of the extremities. The peripheral arteries were thickened.

The temperature was normal. The leucocytes numbered 13,200, with 73 per cent polymorphonuclears. The Wassermann reaction of the blood was negative. The blood urea was 41 mg. per 100 cubic centimeters. A roentgenogram of the heart showed the total transverse diameter to measure 14.2 cm.; the internal diameter of the chest was 26 centimeters.

The following morning he was less cyanotic, but the respirations were shallow. The blood pressure fell to 115/75. He was placed in an oxygen tent and was given digitalis. He died twenty-three hours following admission, after expectorating a mouthful of dark blood.

Clinical Diagnosis.—Interstitial emphysema, postinfectional; chronic bronchitis; myocardial disease due to emphysema; arteriosclerosis of coronary arteries; cardiac insufficiency.

Autopsy No. 11063.—Heart: Weight, 480 grams. Along the auriculoventricular grooves there was a considerable amount of fat. The pericardial surfaces were smooth. The cavity of the right ventricle was slightly enlarged; the ventricular wall was 7 mm. in thickness. The wall of the left ventricle was 20 mm. thick; the cavity of the ventricle was only a little larger than normal. The myocardium was dark-red, coarser than normal, and did not appear scarred. There was moderate hypertrophy of the papillary muscles of the left ventricle. The leaflets of the aortic valves were somewhat thickened in their basal portions, whereas the other parts of the cusps were thin and delicate. The other valves were normal. In the intima of the coronary arteries there were small yellow plaques that were not calcified and did not narrow the lumen.

Aorta: A few scattered yellow areas were seen in the intima of the ascending portion of the vessel. Similar areas were more numerous in the thoracic and abdominal portions; in the latter situation some of the plaques had undergone fatty degeneration, but none was calcified.

Histologic Examination.—Heart: The muscle fibres were larger than normal, their nuclei hyperchromatic and of irregular shapes. The myofibrils were coarse. The muscle coat of the arterioles was somewhat hypertrophied. The veins were distended.

Aorta: The section included one of the largest plaques. The changes were those of moderately advanced sclerosis.

Final Note.—There were no cardiac lesions of any importance. The remaining visceral lesions were trivial, and threw no light on the case.

Anatomic Diagnosis.—Cardiac hypertrophy and dilatation; edema of legs and back; chronic bronchitis; benign hypertrophy of prostate; arteriosclerosis, mild.

CASE 4.—Unit No. 282949. J. R., a Negro man, aged 42 years, single, an elevator operator, was first admitted to the hospital on Jan. 9, 1931, complaining of pain in the abdomen and swelling of the testicles. He had typhoid fever at 12, and pneumonia at 30 years. There were frequent attacks of tonsillitis up to 1921, but none thereafter. He had a chancre when a young man, which was cauterized. He received no other treatment; no other symptoms of syphilis developed. He took one or two drinks of whiskey and smoked fifteen to twenty cigarettes daily. He passed a lodge examination three years earlier.

Ten days previously he noted shortness of breath after mounting two or three flights of stairs. There was also severe pain in the right upper abdominal quadrant, followed, a few days later, by swelling of the scrotum.

Examination showed dyspnea but no orthopnea. The retinal arteries were slightly sclerosed. There were râles at both lung bases. The heart was enlarged. The sounds were faint, with tick-tack quality. The blood pressure was 170/110. The liver was enlarged. There was marked edema of the legs, sacral region, penis, and scrotum.

The Wassermann reaction of the blood, repeated on three occasions, was negative. The spinal fluid Wassermann was likewise negative. There was slight secondary anemia. The leucocytes numbered 10,500, with 65 per cent polymorphonuclears. The blood urea was 21 mg. per 100 cubic centimeters. The electrocardiogram showed regular sinus rhythm; T_1 and T_2 were upright, and T_3 was inverted (Fig. 2). A roentgenogram of the heart showed the transverse diameter to measure 15 cm.; internal diameter of the chest was 25.5 centimeters. The aorta was dilated, particularly in its ascending portion, suggesting aortitis. There were slight fever, up to 99.8° F., and moderate tachycardia; both subsided. Four days after admission the blood pressure was 126/82; subsequently it fell to 115/70.

There was marked improvement following the usual therapy for cardiac insufficiency, and he was discharged at the end of three weeks.

He did not report until Nov. 3, 1933, and gave only a brief account of himself during the interval of nearly three years. He remained up and about. There were almost constant edema and some dyspnea. For four days the symptoms had been markedly accentuated.

Examination was essentially as previously described. The blood pressure was 120/90. There was ascites, as well as edema of the extremities, sacral region, and scrotum. The leucocytes numbered 9,900, with 64 per cent polymorphonuclears. The Wassermann reaction of the blood was again negative. The electrocardiogram was similar to the one taken in 1931. There was no fever.

The patient died suddenly twenty-four hours after admission, with marked dyspnea but no cardiac pain.

Clinical Diagnosis.—Generalized arteriosclerosis; arteriosclerotic heart disease; cardiac hypertrophy due to overstrain; cardiac insufficiency.

Autopsy No. 11373.—Heart: Weight, 500 grams. It was symmetrically hypertrophied. A few grey, nodular thickenings of the epicardium were seen along the branches of the right coronary artery. The epicardium elsewhere was normal, and the subepicardial fat was abundant. The wall of the right auricle was thicker than normal. The tricuspid leaflets were edematous along the free margins. The chordae tendineae were delicate. The cavity of the right ventricle was enlarged. The left auricle was not dilated. Along the line of closure of the anterior cusp

of the mitral valve there was a row of minute, greyish-yellow nodules. The chordae tendineae were normal. The papillary muscles were large, and, beneath the endocardium of the anterior muscle, there was a small, recent hemorrhage. The pulmonic and aortic valves were normal. The endocardium throughout the heart was normal. The myocardium was firm, reddish brown, and somewhat coarsely trabeculated. No scarring could be seen. The wall of the right ventricle measured from 3 to 5 mm. in thickness, and that of the left ventricle, 15 millimeters. Only an occasional, small, sclerotic plaque was found in the intima of the proximal portion of each coronary artery.

Aorta: A few atherosclerotic plaques were present.

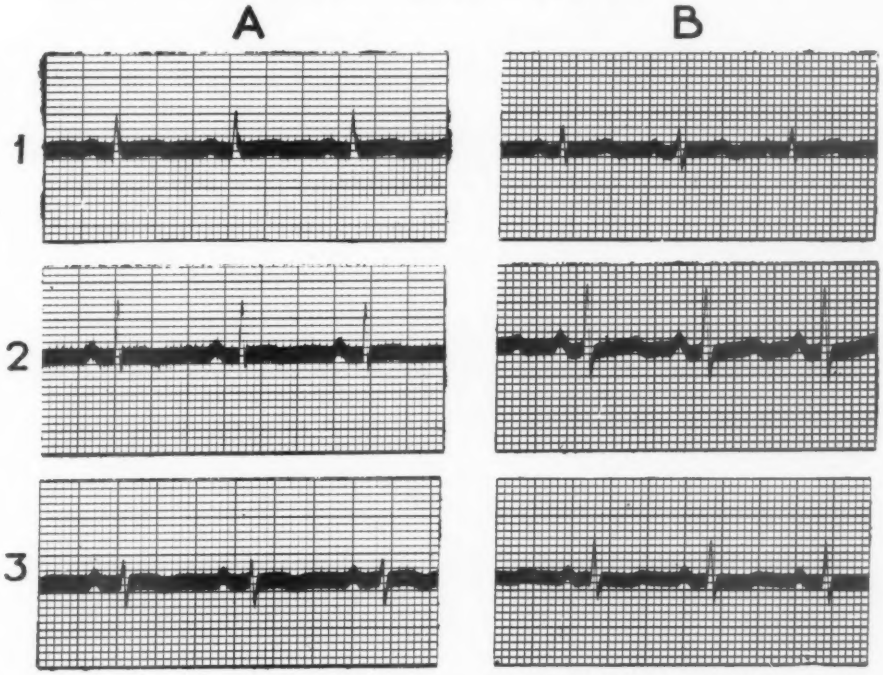


Fig. 2.—Electrocardiograms in Case 4. *A*, Jan. 10, 1931: sinus rhythm; rate 98. P-R = 0.16 second. T waves are of low amplitude in Lead I; inverted in Leads II and III. Patient received 0.9 Gm. of digitalis on preceding day. *B*, Nov. 4, 1933: slight alterations in T waves, due probably to absence of digitalis effect. No changes indicating serious myocardial damage. Patient died suddenly ten hours after this record was taken.

Histologic Examination.—Heart: The myocardium was hypertrophied, and the nuclei were hyperchromatic. There was no scarring. The intima of an occasional small branch of the coronary arteries was slightly thickened, whereas that of a larger branch was moderately thick, but the lumen was very little reduced in size and the heart muscle supplied by it was intact. Section through one of the nodules on the mitral valve did not disclose any evidence of rheumatic disease.

Aorta: The intima was uniformly and moderately thickened by fibrillar material. The media and adventitia were normal.

Final Note.—No explanation was forthcoming for the very decided cardiac hypertrophy, especially of the right ventricle. There was only one blood pressure reading; it indicated hypertension two years before,

but the recent measurements had been low. Aside from the lack of positive data, no arteriolar lesions of any significance were found to support a diagnosis of hypertensive disease.

Anatomic Diagnosis.—Cardiac hypertrophy and dilatation; chronic passive congestion of viscera; edema of lungs; anasarca; ascites; ulcer of stomach, healed.

CASE 5.—Unit No. 34039. H. S., a white man, aged 67 years, single, a porter, was first admitted to the hospital on Feb. 15, 1917, complaining of dyspnea. He was born in Germany and worked there on a farm. At 27 years, he had smallpox. For six years he worked around the Presbyterian Hospital as porter and handy man. He took two beers daily and a drink of whiskey before breakfast, as well as an occasional glass of wine. He smoked two pipes a day and an occasional cigar.

For one month he had noted difficulty in breathing on climbing stairs. This became progressively more marked and work was impossible. Soon after dyspnea appeared,his feet began to swell. There was no cardiac pain.

Examination showed moderate dyspnea. The lungs were normal. The heart was markedly enlarged. The sounds were faint. The rhythm was regular. No murmurs were heard. There was slight edema of the legs and feet.

The temperature rose to 100.4° F. on the second day, but returned promptly to normal. The blood pressure was 150/92. There was no anemia. The leucocytes numbered 6,500, with 74 per cent polymorphonuclears.

After six days he was discharged, improved. He worked around the hospital for two and one-half weeks and was then again admitted with the same complaints and similar findings. He improved after a rest of ten days.

His final admission was on March 29. During the eight days after his discharge he remained quiet, but dyspnea and edema recurred. A liter of fluid was removed from the right pleural cavity and 500 c.c. from the left. Gallop rhythm appeared. The temperature rose to 102.4° F. The blood pressure was 132/96. He failed to improve, and died, ten days after admission, of progressive myocardial insufficiency.

Clinical Diagnosis.—Chronic myocarditis; chronic bronchitis; cardiac insufficiency.

Autopsy No. 8704.—Heart: Weight, 620 grams. The epicardium was thickened and white over a large area on the right ventricle. In the right auricular appendage there were some small thrombi. The endocardium of all the chambers was normal. The tricuspid and pulmonary valves were normal. The mitral leaflets were somewhat thickened along the free border; the aortic cusps were moderately sclerotic at their bases, although the upper portions were thin and delicate. At the apex of the left ventricle and over the septum there were several large thrombi; the largest of these was almost 1 cm. in its greatest diameter. The endocardium beneath these thrombi was not thickened. The myocardium was coarse; its color and texture were normal, and there was no evident scarring. The right ventricular wall measured 2 to 4 mm. in thickness; the left, 14 to 16 millimeters. The coronary arteries were slightly tortuous and were almost free of atheroma.

Aorta: Above the sinuses of Valsalva there were a few small sclerotic plaques.

Histologic Examination.—Heart: The muscle fibers were hypertrophied; the nuclei were larger than normal, of irregular shapes, and

frequently hyperchromatic. In a few very small areas there was a trifling increase of connective tissue between the myocardial fibers. A section through the tip of one of the papillary muscles of the left ventricle disclosed some scarring of the myocardium, with pigment-containing phagocytes in the scar. The muscle adjacent to the scar was vacuolated. The thrombi in the left ventricle were, in part, of very recent formation, but in other portions they were older, and showed beginning organization. The endocardium and myocardium were unaltered beneath the thrombi except for those changes incident to their organization.

Aorta: The intima was slightly thickened by fibrillar tissue; the media and adventitia were normal.

Anatomic Diagnosis.—Cardiac hypertrophy; thrombi in auricle, right, and ventricle, left; infarcts of lung and kidney; chronic passive congestion of viscera; hydrothorax, bilateral; edema of lungs; benign hypertrophy of prostate.

CASE 6.—Unit No. 59224. W. J., a white man, aged 53 years, married, a dock laborer, was admitted to the hospital on Feb. 16, 1924, complaining of swelling of the legs and abdomen. He had pneumonia at 15 years of age. For about fifteen years he suffered from attacks of asthma, chiefly at night, and worse during hot weather. Asthma powders afforded relief. There was no history of venereal disease. He took an occasional drink, but never imbibed excessively. For eight or ten years he had been short of breath on climbing stairs. He worked up to the onset of the present illness.

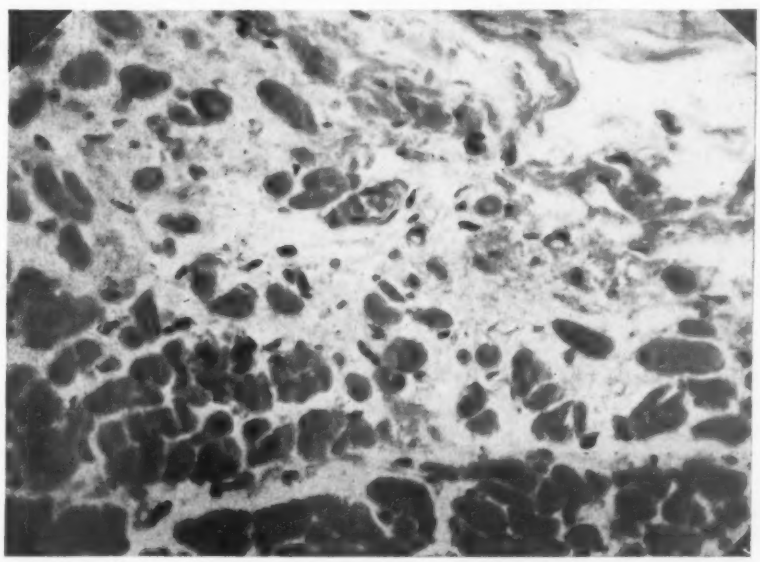


Fig. 3.—Case 6. Hypertrophy of myocardium with slight fibrosis.

Eight weeks before, he had a sharp pain in the right lower portion of the abdomen, relieved by heat. His abdomen soon began to swell, and dyspnea became so severe that he was obliged to sleep in a chair. Five days before admission his feet and legs became swollen; the swelling increased rapidly. Asthmatic paroxysms were accompanied by

pain in the region of the sternum and precordium. Attacks of cough and dyspnea caused palpitation.

Examination showed dyspnea, orthopnea, cyanosis, and marked edema of the legs, sacral region, genitals, and abdomen. Ascites was present. The heart was greatly enlarged. The rhythm was irregular; the rate, 120. The sounds were of poor quality and a loud gallop was heard. There were no murmurs. There were a few râles at the bases of the lungs. There was no peripheral vascular sclerosis. The blood pressure ranged from 110 to 150 mm. Hg, systolic, and 70 to 90, diastolic.

The temperature was 101° F. on admission, and ranged thereafter from 99 to 101.2°. A roentgenogram of the heart showed the transverse diameter to measure 17.6 cm.; the internal diameter of the chest was 31 centimeters. There was some widening of the aortic shadow. The electrocardiogram showed auricular fibrillation, with occasional ventricular ectopic beats. The T wave was inverted in Leads I and II, and upright in Lead III. Left axis deviation was present.

After rest and digitalis therapy, the heart rate fell to between 50 and 60, and there was clinical improvement. On the second day after admission, while sitting in a chair, he suddenly became dyspneic and cyanotic, and died quickly, without evidence of pain.

Clinical Diagnosis.—Chronic myocarditis; cardiac hypertrophy; auricular fibrillation; cardiac insufficiency; thrombosis of coronary artery.

Autopsy No. 9493.—Heart: Weight, 600 grams. Several small areas of thickening were present in the epicardium of the left ventricle. The mitral and aortic valve leaflets were slightly thickened, although not incompetent; the tricuspid and pulmonic valves were normal. The chordae tendineae were unaltered. The wall of the left ventricle was thickened. In the coronary arteries there were a few sclerotic plaques.

Aorta: Many large and small, elevated, yellowish-white areas were present in the intima.

Histologic Examination.—Heart: The myocardial fibers were larger than normal; the nuclei were of irregular shapes, large and hyperchromatic. Only rarely was any scarring found; this was insignificant and consisted of an increase of collagen between the muscle (Fig. 3). An occasional arteriole showed moderate eccentric thickening of its intima by fibrillar tissue. A small, fresh, endocardial hemorrhage was present in the left ventricle.

Aorta: The intima was thicker than normal, and fat-containing phagocytes, in moderate numbers, were seen in it. The media and adventitia were unaltered.

Final Note.—The pathologic study offered no explanation for the sudden death.

Anatomic Diagnosis.—Arteriosclerosis; cardiac hypertrophy; emphysema, mild.

CASE 7.—Unit No. 69800. S. R., a white man, aged 29 years, married, was first admitted to the hospital on Sept. 17, 1927, complaining of palpitation. He had been an automobile mechanic for twelve years and enjoyed unusually good health. He had gonorrhea at 20 years of age, but denied syphilis. His consumption of alcohol and tobacco was very moderate.

He first was conscious of cardiac irregularity five years previously, while working in South America. The irregular and rapid beating of his heart occurred in paroxysms lasting from five to fifteen minutes.

The attacks increased in frequency, and for two and one-half months tachycardia had persisted almost continuously.

Examination showed a large, well-developed man. There was no dyspnea or cyanosis. The lungs were normal. The heart was considerably enlarged. The rate was variable, at times 120 to 160 per minute, with regular rhythm, then a few irregular beats, followed by a sudden drop to 60. The sounds were of moderate intensity. There was splitting of the first sound at the apex. No murmurs were heard. The peripheral vessels were not thickened. The blood pressure was 110/80. The liver was not enlarged. There was no clubbing of the fingers. No edema was present.

The temperature was normal and remained so throughout his stay in the hospital. The leucocytes numbered 12,000, with 63 per cent polymorphonuclears. There was no anemia. The Wassermann reaction of the blood was negative. The urine contained a faint trace of albumin. The total transverse diameter of the heart measured 17.8 cm., the great vessels, 6 cm., and the internal diameter of the chest, 30.5 centimeters.

The heart rate varied greatly from day to day and from hour to hour. The dominant rhythm was a tachycardia which had its origin in the junctional tissues, with a rate of 50 to 160. Numerous ventricular premature beats occurred. The P-R interval, when it could be measured, varied from 0.22 to 0.31 second, and there was widening of QRS when nodal rhythm, with a slow rate, was present. The T wave was inverted in Lead I and upright in Leads II and III.

The administration of quinidine, by mouth, did not affect either the rate or the rhythm. The use of digitalis, first in full doses, and then in maintenance ration, slowed the rate to 60, with occasional short paroxysms of tachycardia during which the rate rose to 120. The blood pressure rose to 130/70. On discharge, after four weeks in the hospital, the patient felt greatly improved, and was instructed to continue with small, daily doses of digitalis.

He was lost sight of until eight months later, when he came to the clinic desperately ill. After discharge from the hospital he again went to South America on a job, but had to quit work after five weeks because of recurrence of the paroxysms of tachycardia. He returned to this country two weeks before admission, and since that time had had great difficulty in getting his breath.

On the second admission, June 4, 1928, he was cold, and a clammy sweat covered the skin. The respirations were rapid and shallow. The pulse was barely palpable. The heart rate was about 180, and the rhythm was apparently regular. The temperature was 99.4° F. The blood pressure was 134/90. The Wassermann reaction of the blood was again negative. A blood culture showed no growth. The leucocyte count was 13,000, with 42 per cent polymorphonuclears. There was no anemia. The blood urea was 41 mg. per 100 cubic centimeters. Electrocardiograms showed, at times, auricular tachycardia with a rate of 170 and incomplete bundle branch block, and, at other times, A-V nodal rhythm with a rate of 70 to 80, with complete bundle branch block and numerous ventricular premature beats. When the rate was slow, QRS measured 0.17 second; R was notched and T was inverted in all leads. The records were very different in form from those previously obtained.

Dyspnea persisted and was more marked during the paroxysms of tachycardia. The administration of large doses of digitalis was with-

out apparent benefit. He began spitting up blood, evidently as a result of pulmonary infarction. The temperature rose to 103.4° F., and the leucocyte count to 31,000, with 79 per cent polymorphonuclears. Orthopnea and prostration became extreme, and he died on June 10, six days after entering the hospital.

Clinical Diagnosis.—Cardiac hypertrophy; chronic cardiac dilatation; infarct of heart; cardiac insufficiency; paroxysmal tachycardia; infarct of lung; premature contractions, auricular and ventricular; trypanosomiasis?

Autopsy No. 10017.—Heart: Weight, 740 grams. The chambers of the heart were greatly dilated. There was hypertrophy of the columnae carneae and papillary muscles of each ventricle. At the apex of the left ventricle the wall was thin; elsewhere it was hypertrophied, as was that of the right. The right ventricle measured 0.6 cm. in thickness, and the left ventricle, 2.4 cm., except at the apex, where it was 0.5 centimeters. The only scarring found was in the posterior papillary muscle of the left ventricle. Between the columnae carneae of the left ventricle there were several small thrombi. The valves were essentially normal. The chordae tendineae were unaltered. In the anterior descending branch of the left coronary artery there were many small areas of sclerosis; the coronary arteries were otherwise normal.

Aorta: Normal except for small sclerotic areas near the origin of the branches.

Histologic Examination.—Heart: The myocardium was hypertrophied. Areas of necrosis were present. In some places the muscle was degenerating; in other portions it had been replaced by connective tissue. A dense band of fibrous tissue was found in the myocardium of the septum just beneath the endothelium; it was infiltrated with mononuclear cells. In some places the endocardial surface was covered with small thrombi.

Final Note.—Cardiac hypertrophy and dilatation were the dominant features of the post-mortem examination. There were no inflammatory or degenerative lesions in any part of the cardiovascular system. The various embolic phenomena were secondary to the cardiac thrombi. After careful study of all of the material, no etiological basis for the heart lesion could be found.

Anatomic Diagnosis.—Cardiac hypertrophy and dilatation; infarcts of heart, old and recent; fibrous thickening of endocardium of ventricle, left; thrombi in ventricle, left; infarcts of lungs; infarct of kidney, right; hydrothorax, right; edema of lower extremities; chronic passive congestion of viscera; congenital malformation of aorta (common origin of innominate and left common carotid arteries).

Case 8.—Unit No. 497583. F. L., a white woman, aged 66 years, a housewife, was admitted to the hospital on Sept. 5, 1936, complaining of dyspnea and "heart attacks." She was never strong. She had diphtheria at 7 years of age and pneumonia at 20 and 21 years of age. She was said to have had tuberculosis at 23 years, cured after a year spent in India. Perineorrhaphy was performed at 38, and again at 41, years. Several bones had been broken in a motor car accident ten years before. She neither drank alcohol nor used tobacco.

After the attack of diphtheria at 7 years, she had generalized dropsy which confined her to bed for a year. No information concerning the heart or kidneys was available. Thereafter, she was considered well, but not robust. She always became easily winded on

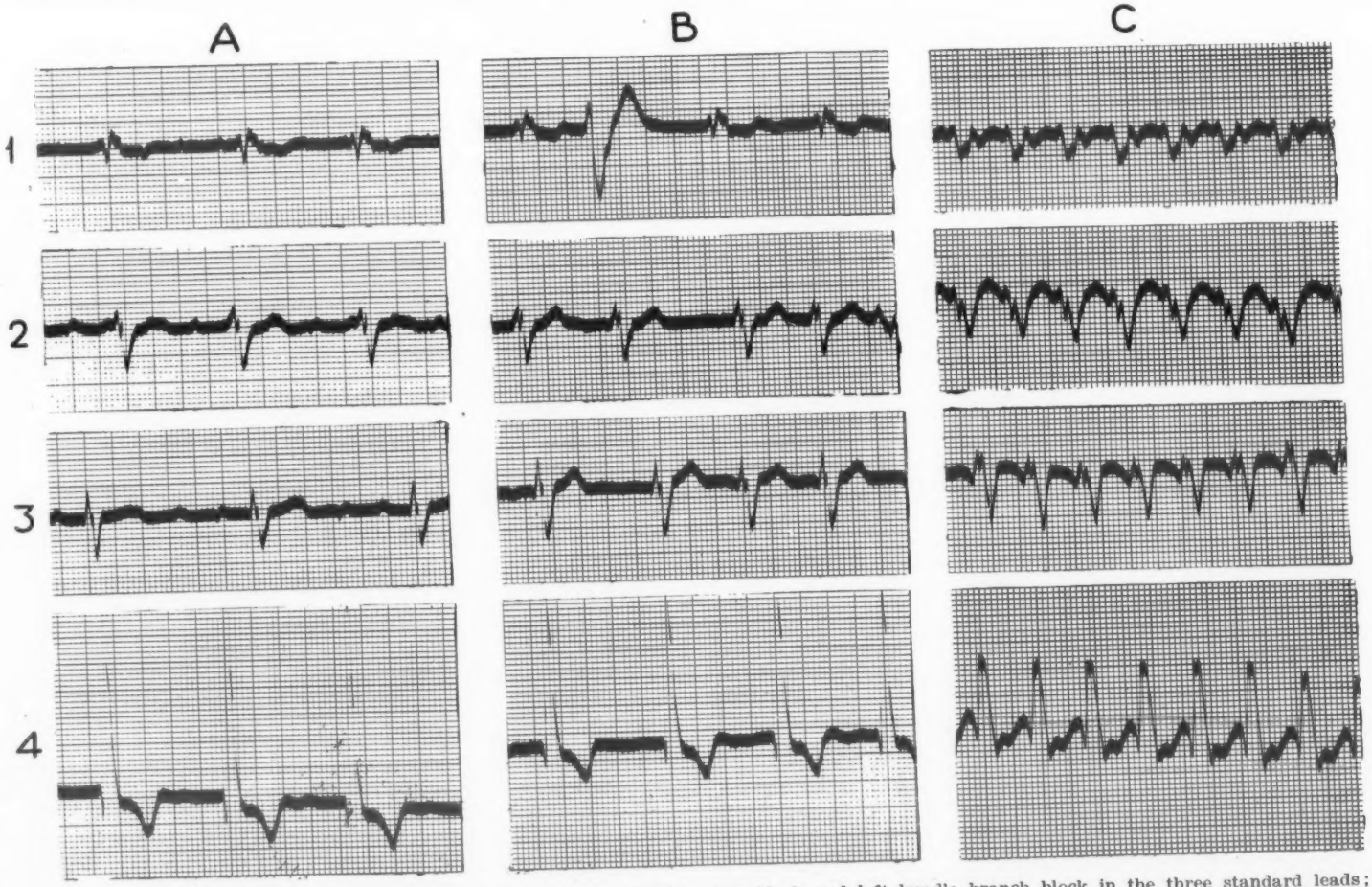


Fig. 4.—Electrocardiograms in Case 8. *A*, Aug. 15, 1936: complete A-V block and left bundle branch block in the three standard leads; auricular rate 130; ventricular rate 58. In Lead IV,* auricular fibrillation is present, with more rapid ventricular rate. The record indicates advanced myocardial damage. No digitalis or quinidine had been given. *B*, Oct. 16, 1936: auricular fibrillation, ventricular premature beats and left bundle branch block; ventricular rate 75. The general form of the ventricular complexes shows no marked change. *C*, Nov. 10, 1936: ventricular tachycardia; rate 160. Patient died twenty-two hours later.

*The precordial electrode was at the apex, the indifferent electrode on the left leg. T_4, according to the technique used, was normally inverted.

playing games. At 52 years of age, she was told that her heart was large, but she was not incapacitated. The blood pressure had been taken repeatedly and was always said to be normal. Seven years before, an electrocardiogram showed no abnormal changes. For the preceding six years she had been under the observation of Dr. H. E. B. Pardee, who found cardiac enlargement, intraventricular block in the electrocardiogram, and, under the fluoroscope, saw a knoblike shadow projecting from the right side of the heart. There were no evidences of congestive failure.

Six months before admission she suddenly developed an attack of precordial oppression and dyspnea. The heart rate was over 200. At the end of an hour, and after a hypodermic injection, it fell to 90. After that attack she was a cardiac invalid, and had dyspnea, edema, and three attacks of pulmonary congestion with fever up to 103° F. She had taken digitalis, scillaren, and ammonium chloride.

Examination showed dyspnea, but no cyanosis. There was slight edema of the ankles and sacral region. There were crackles at the bases of both lungs. The heart was enlarged, extending to the left anterior axillary line. The rhythm was regular, the rate, 42. The sounds were of fair quality; a soft systolic blow was heard at the apex. The liver was markedly enlarged. The radial arteries were thickened. The blood pressure on admission was 140/105. Subsequent readings ranged from 135 to 116, systolic, and 90 to 66, diastolic.

The blood cell count was normal. The Wassermann reaction of the blood was negative. The blood urea was 35 mg. per 100 cubic centimeters. A roentgenogram of the heart showed the transverse diameter to measure 17.2 cm.; the internal diameter of the chest was 22.3 centimeters. There was slight calcification of the aortic knob. Fluoroscopic examination showed a hump in the contour of the right border anterolaterally, suggesting to the roentgenologist an aneurysm of the right ventricle or an intrapericardial aneurysm low in the aorta. The electrocardiogram, on admission, showed sinus rhythm with prolonged A-V conduction and left bundle branch block. The P-R interval was 0.33 second, QRS, 0.15 second. The T wave was inverted in Leads I and II, upright in Lead III, and inverted in Lead IV. During the period of observation, complete A-V heart block developed, with, at times, auricular fibrillation and flutter. There were also paroxysms of ventricular tachycardia, which responded to quinidine therapy (Fig. 4).

For a time, myocardial function improved. A skin rash appeared, and was regarded as a toxic dermatitis of unknown cause. The temperature for several weeks ranged from normal to 100.2° F., rising shortly before death to 104.4°. The cause of the fever was unexplained. A blood culture was negative. Two days before death, there were signs of right hemiplegia with left facial palsy. Two months after entering the hospital she died during a paroxysm of ventricular tachycardia.

Clinical Diagnosis.—Arteriosclerotic heart disease; cardiac hypertrophy; cardiac insufficiency; bundle branch block; auricular fibrillation; auricular flutter; ventricular tachycardia; embolus to right lenticulostriate artery by infected thrombus; undiagnosed condition of skin; fever of unknown origin.

Antopsy No. 12274.—Heart: Weight, 440 grams. It was uniformly enlarged; the apex was formed by both ventricles, but principally by the left. Many subepicardial petechiae were seen along the distribution of the coronary arteries over the ventricles. All of the chambers

of the heart were enlarged. The walls of the auricles did not appear to be hypertrophied; those of the ventricles were somewhat thickened, that of the right ventricle measuring 5 mm., the left, 15 millimeters.

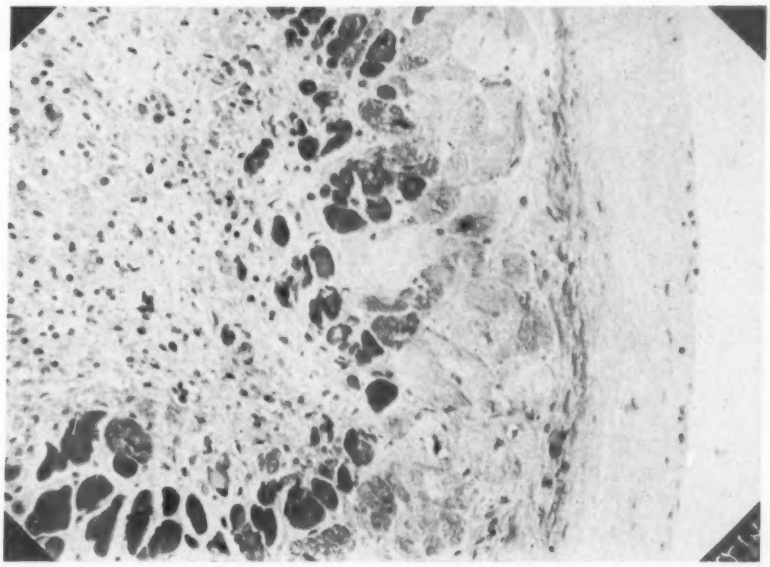


Fig. 5.—Case 8. Hypertrophy and necrosis of myocardium. Necrosis extends into conduction bundle (section from interventricular septum).

Fig. 6.—Case 8. Hypertrophy of myocardium and scar of an area of previous necrosis.

All of the papillary muscles were moderately enlarged. The tricuspid, pulmonic, and mitral valves were normal; the chordae tendineae were delicate. There was some thickening of the base of each aortic cusp;

the remaining portion of the leaflets was normal. The myocardium of both ventricles was firm and reddish-brown. Fine, greyish streaks were present in the myocardium of the left ventricle, and the septal muscle was mottled with yellowish-grey areas. The endocardium over the septum was thickened below the aortic valve; elsewhere it was normal. Only a few, very small, yellowish areas were found in the intima of the coronary arteries.

Aorta: Small, slightly raised, yellowish-grey plaques were present in the intima of the ascending portion. Similar areas were more numerous in the abdominal segment of the aorta, where a few of them were ulcerated.

Histologic Examination.—Heart: The myocardium of both auricles was hypertrophied and diffusely scarred. In the right ventricle there were areas of recent necrosis where the muscle was homogeneous, stained deeply with eosin, and did not show any nuclei. These necroses frequently involved the branches of the conduction system.

Numerous areas of necrosis were seen in the interventricular septum. These areas were of variable size, and often extended into the conduction bundle (Fig. 5). In addition, there were scars composed of loose connective tissue (Fig. 6). Phagocytes filled with pale-yellow, granular pigment were present in the scars. Changes similar to those in the septum occurred in the left ventricle and papillary muscle, and the necroses and scars frequently extended into the conduction fibers.

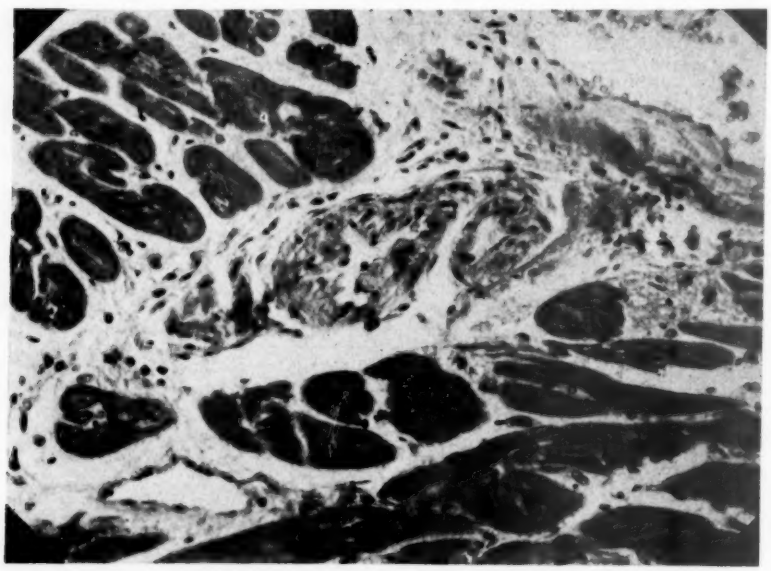


Fig. 7.—Case 8. Slight sclerosis of arteriole in myocardium.

In all of the sections, aggregates of small mononuclear cells were clustered about or near some of the arterioles. Only rarely was there an arteriole with a thickened intima, and in such arterioles this alteration was slight; it did not affect the entire intima, and the lumen was not appreciably narrowed (Fig. 7).

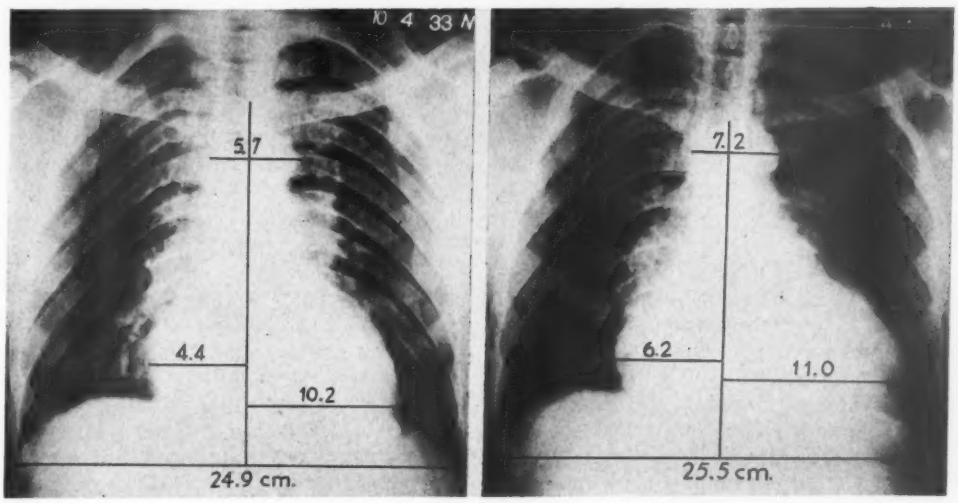
Aorta: The only lesion was that of moderately advanced atherosclerosis.

Final Note.—This was an interesting and rather obscure case of an elderly woman who for a number of months had had attacks of parox-

ysmal tachycardia and, toward the end of her life, electrocardiographic changes showing, at times, complete, and at other times, partial, heart block. The case was looked upon as one of coronary sclerosis and myocardial damage, but this was not confirmed by the autopsy. In both ventricles there were numerous patches of recent necrosis with little or no cellular reaction, together with older and more recent scars. There was a history of diphtheria followed by edema and temporary cardiac embarrassment. This occurred when the patient was 7 years old, and there was a long interval during which she was free from cardiac symptoms. It seemed farfetched to refer the myocardial scars to a past diphtheritic myocarditis, and certainly one must seek another explanation for the recent necroses.

Anatomic Diagnosis.—Necroses of myocardium, healed and recent; cardiac hypertrophy and dilatation; chronic passive congestion of lungs; lobular pneumonia, confluent; focal necroses of liver; acute splenic tumor; encephalomalacia, internal capsule, left; toxic erythema; infarcts of kidneys, healed; cholelithiasis.

CASE 9.—Unit No. 392348. T. I., a Negro man, aged 38, married, an unemployed longshoreman, was first admitted to the hospital on Sept. 25, 1933, complaining of shortness of breath, cough, and attacks of nocturnal dyspnea. His general health was good. At the age of 18 years he had a chancre, and also gonorrhea with inguinal abscesses. Specific intravenous therapy was given for a short time. He was refused for Army service in 1918 (aged 23 years) because of "heart trouble." He was in the habit of drinking plenty of whiskey, but the amount was not stated.



A. *B.*

Fig. 8.—Case 9. Teleroentgenograms showing increase in size of heart in course of two and one-half years. *A*, Oct. 4, 1933: two months after onset of symptoms. *B*, April 24, 1936: six months before death.

Six weeks before admission, dyspnea, cough, and nocturnal attacks of asthma began and increased rapidly in severity. For three weeks the ankles and legs had been swollen.

Examination showed moderate dyspnea on effort. There were râles at the bases of both lungs. The heart was enlarged. The rhythm was

regular save for a few premature beats. A gallop was heard. The liver was enlarged. There was brawny edema of the legs up to the mid-thighs; the scrotum was swollen. The blood pressure was 120/85. The retinal vessels were not sclerotic.

The Wassermann and Kahn reactions of the blood were strongly positive. The spinal fluid Wassermann was negative. An electrocardiogram showed sinus rhythm with low voltage. The P-R interval measured 0.17 second. The T wave was inverted in the three standard leads. The blood cell count was normal. A roentgenogram of the heart showed the transverse diameter to measure 14.6 cm.; the internal diameter of the chest was 24.9 cm. (Fig. 8). The sedimentation rate of the erythrocytes was 19 mm. in one hour. There was no fever. The blood pressure fell to 90/70; on discharge it was 104/72.

The usual cardiac therapy was followed by improvement. Intramuscular injections of bismuth were begun, and iodide was given by mouth. He was sent home at the end of five weeks, with compensation recovered.

In the course of the next three years, the patient was admitted to the hospital five times at intervals of several months, on each occasion with myocardial insufficiency. Antisyphilitic treatment was continued in the out-patient department, in courses. In December, 1934, bundle branch block appeared for the first time in the electrocardiogram. Low voltage was no longer present. The QRS interval measured 0.12 second. The T wave was inverted in Lead I and upright in Leads II and III. Bundle branch block persisted from this time until death, with occasional premature beats interrupting the regular rhythm (Fig. 9). The gallop also continued to be heard. The blood pressure remained low. The Wassermann reaction was always strongly positive.

On April 10, 1936, one of us (R. L. L.) made the following note: "Symptoms began at the age of 38 years. There has been no consistent elevation of blood pressure. The evidence for the existence of a syphilitic myocarditis is slender; by most pathologists, this form of diffuse myocarditis is not recognized. Coronary sclerosis is a possibility, although because of the course, is unlikely to be present. Cardiac enlargement has always been conspicuous. The electrocardiographic changes and repeated attacks of congestive failure indicate a seriously damaged myocardium. The blood pressure today is 114/90. There is a marked protodiastolic gallop.

"This case, it seems to me, must be classed in the group described as 'hypertrophy of unknown etiology,' in which the lesions in the heart muscle vary in character and degree. The immediate prognosis for this bout is good. Within two years, I believe the course will be run."

The final admission was on Oct. 20, 1936. Congestive failure was marked. The temperature rose to 102.8° F. There were signs of diffuse, bilateral bronchopneumonia. The leucocytes numbered 14,500, with 84 per cent polymorphonuclears. He was irrational and failed steadily. He died thirty hours after entering the hospital, at the age of 42, having had symptoms for a little over three years.

Clinical Diagnosis.—This varied on different admissions to the hospital. The following were included: Syphilis; syphilitic aortitis; narrowing of coronary artery due to syphilis; generalized arteriosclerosis; arteriosclerotic heart disease; sclerosis of coronary arteries; fibrosis of myocardium; cardiac enlargement; cardiac insufficiency; syphilitic myocarditis; bronchopneumonia, organism unknown.

Autopsy No. 12256.—Heart: Weight, 570 grams. The epicardium was thickened over the coronary arteries. The cavities of the right

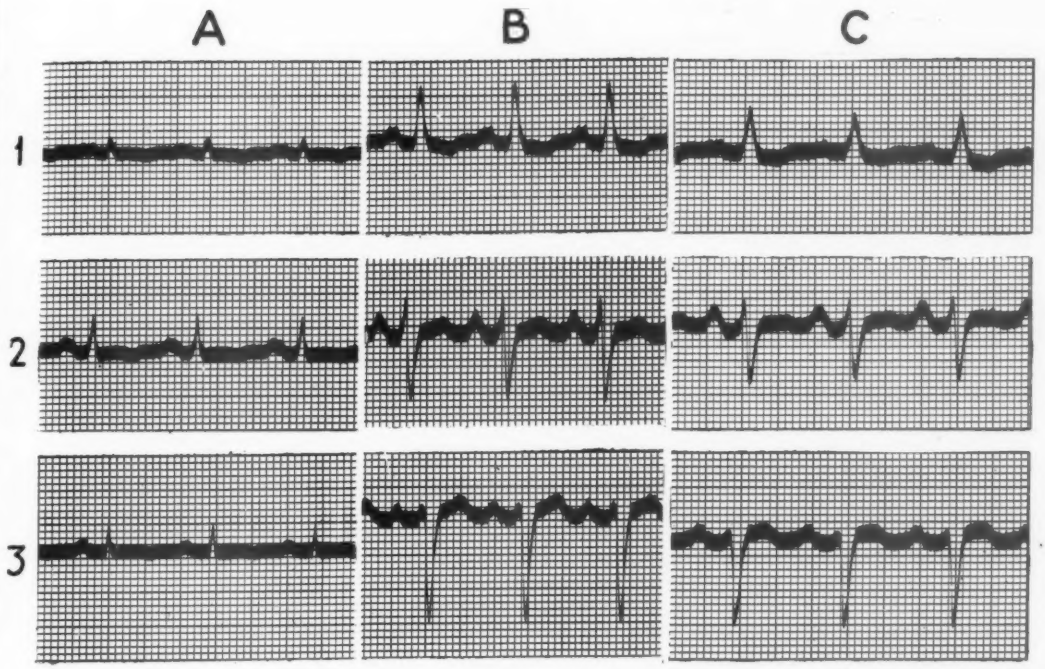


Fig. 9.—Electrocardiograms in Case 9. *A*, Sept. 26, 1933: sinus tachycardia; rate 108. P-R = 0.16 second. Low voltage, with inversion of T waves in all leads. No digitalis taken. *B*, Dec. 29, 1934: left bundle branch block; rate 100. P-R = 0.16 second; QRS = 0.12 second. Conspicuous changes have occurred since record made three months earlier. *C*, Aug. 11, 1936: left bundle branch block; rate 90. P-R = 0.20 second; QRS = 0.12 second. Only slight changes have taken place since record made nineteen months before. Patient died three weeks later.

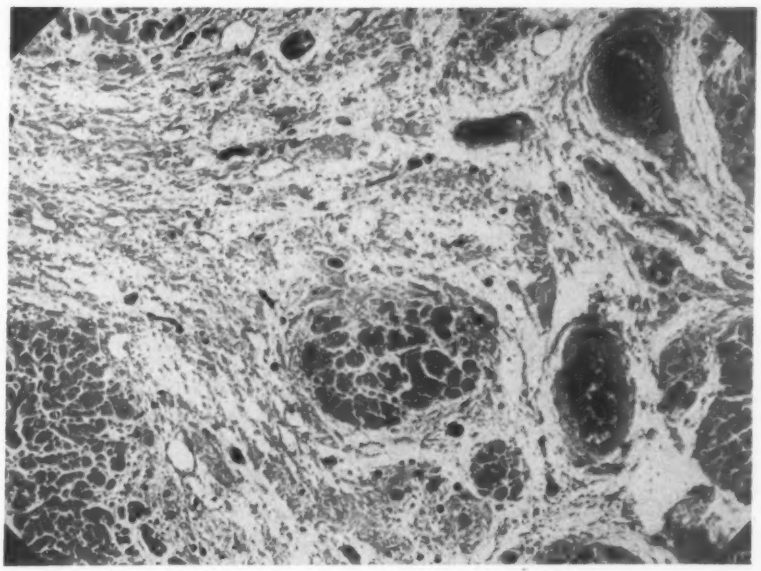


Fig. 10.—Case 9. Hypertrophy of myocardium with fibrosis.

auricle and ventricle were greatly dilated. In the auricular appendage there was a small thrombus. The tricuspid and pulmonic valves were normal. The left auricle was markedly dilated. The edges of the mitral leaflets, at the right juncture of the cusps, were moderately thickened. A few of the chordae tendineae inserting into these parts of the leaflets were thickened; the other chordae were normal. The papillary muscles were moderately hypertrophied. The aortic valve was normal. The myocardium was a pale, greyish red, with many pinkish-grey scars in the left ventricle. Below the aortic ring there was a greyish-white scar, 2 cm. in diameter. The wall of the right ventricle was 6 mm. thick, and that of the left, 14 to 20 millimeters. The coronary arteries were strikingly free of atheroma and were entirely normal.

Aorta: There was surprisingly little atheroma; only a few fatty plaques were found in the abdominal portion of the vessel.

Histologic Examination.—Heart: The myocardium was hypertrophied. Scars of varying sizes were found in the walls of both ventricles and the interventricular septum. The scars were compact, and but slightly vascularized (Fig. 10). Near the vessels at the margins of the scars there were sparse collections of lymphocytes. The arteries and arterioles were normal. The thrombus in the right auricular appendage was in process of being organized. The myocardium beneath the thrombus was hypertrophied but not scarred.

Aorta: The intima was slightly thickened by fibrillar material. The media and adventitia were normal.

Final Note.—There were none of the obvious causes of myocardial fibrosis, neither syphilis, coronary sclerosis, nor clear evidence of old rheumatic disease. There was no syphilitic aortitis. One is driven to assume that the lesions represented healed myocarditis of unknown cause.

Anatomic Diagnosis.—Myocarditis, obsolete (?); fibrosis of myocardium; cardiac hypertrophy and dilatation; thrombus in auricle, right; infarct of lung and spleen; chronic passive congestion of viscera; encephalomalacia, cerebellum, right; ascites; hydrothorax, bilateral; edema of ankles; cholelithiasis.

Case 10.—Unit No. 259359. E. S., a Negro man, aged 43 years, married, a porter, was first seen in the Vanderbilt Clinic on June 12, 1930, complaining of epigastric pain. He had pneumonia at 41, and a chancre at 42 years of age, for which five or six treatments were given. He took a pint of whiskey daily from 1900 to 1929; for the preceding six months he had taken three drinks a day and had gone on a drunken spree every two weeks. He smoked thirty cigarettes and chewed a plug of tobacco daily. Three months previously he noted dyspnea on effort and abdominal pain. He had lost 20 pounds in four years.

Examination showed an enlarged heart, with gallop rhythm at the apex. There were moist râles at the bases of both lungs. The liver was large and tender. The blood pressure was 96/80.

The Wassermann reaction of the blood was positive (2 plus with the alcoholic antigen and 4 plus with the cholesterin antigen). A roentgenogram of the heart showed the transverse diameter to measure 16.3 cm.; the internal diameter of the chest was 24 centimeters. The electrocardiogram showed sinus rhythm with left blundle branch block.

He received five courses of bismuth by intramuscular injection between July, 1930, and July, 1933. He was also given digitalis and

potassium iodide. During these three years he got along fairly well, although he was unable to work because of exacerbations of dyspnea and precordial pain. Frequent, severe, sore throats and cough aggravated the symptoms. For this reason, in December, 1932, tonsillectomy was performed. At that time, the electrocardiogram resembled the one made eighteen months previously. The heart was larger. The blood pressure ranged from 130 to 90, systolic, and 80 to 60, diastolic. The basal metabolic rate was −5 per cent.

There were three subsequent admissions to the hospital on account of recurring and progressively severe myocardial insufficiency. The blood urea was slightly elevated during decompensation, but returned to normal after improvement. The form of the electrocardiogram did not change. The Wassermann reaction was now negative; the Kahn reaction was faintly positive. The levels of the blood pressure were as described. On one occasion he coughed up bloody sputum and there was elevation of temperature, presumably because of pulmonary infarction.

Fig. 11.—Case 10. Hypertrophy of myocardium with fibrosis.

He was brought to the hospital on Nov. 12, 1934, in a semicomatose condition. Hyperpnea was marked. The venous pressure was 16 cm. of water. The leucocyte count was 19,500. He presented the picture of shock. The temperature rose steadily to 105° F., and he died in coma five days after entering the ward and four and one-half years after the onset of symptoms.

Clinical Diagnosis.—Enlarged heart, cause unknown; infarction of myocardium due to arteriosclerotic coronary thrombosis; infarction of lungs, embolic; bronchopneumonia; Wassermann reaction, positive.

Autopsy No. 11665.—Heart: Weight, 490 grams. It was very large as compared with the size of the body. The apex was formed by the left ventricle. Many small recent hemorrhages were seen beneath the epicardium of the auricles and their appendages. The right auricle

and ventricle were dilated. At the apex, the wall of the right ventricle measured only 1 mm. in thickness, although in other parts the ventricular wall was as much as 8 mm. thick. A thrombus was found at the apex between the columnae carneae. The tricuspid and pulmonic valves were normal. The left auricle was moderately dilated. The left margin of the anterior leaflet and the adjacent portion of the posterior cusp of the mitral valve were thickened, and the chordae tendineae inserting into these parts of the leaflets were thicker than normal. The papillary muscles were hypertrophied. The left ventricle was enormously dilated; its wall measured from 12 to 20 mm. in thickness. At its apex the columnae carneae were thinner than normal. The aortic cusps were slightly thickened in their basal portions. The endocardium throughout the heart was normal except for some opaque streaks and yellowish areas over the septum of the left ventricle. The myocardium was brownish red and had a coarse texture. Except for some tortuosity, the coronary arteries were normal.

Aorta: A few yellowish, atheromatous plaques were present in the intima of the posterior wall.

Histologic Examination.—Heart: In all of the sections the myocardium showed the usual characteristics of hypertrophy. One section from the left ventricle passed through an area in which the muscle had been replaced by a broad, compact scar in which there were only a few capillaries (Fig. 11). Near the margin of the scar was a small vein with an accumulation of lymphocytes about it. In a second section collagen separated the myocardial fibers, but did not replace any of them. On the endocardial surface there was an organizing thrombus. The muscle beneath the thrombus was unaltered except for hypertrophy.

A section from the apex of the right ventricle disclosed diffuse scarring of the myocardium near the epicardial surface. The endocardial thrombus was in process of being organized. The myocardium immediately beneath the thrombus was diffusely infiltrated with small mononuclear cells, but was not scarred. In all of the sections the coronary arterioles were normal.

Aorta: The media and adventitia were normal. The intima was moderately thickened by fibrillar tissue.

Final Note.—This case seems to fall into the category of unexplained cardiac fibrosis, with hypertrophy and dilatation. All of the usual causes of cardiac hypertrophy could be excluded, namely, hypertension, renal disease, thyroid disease, and syphilis. The coronary arteries and arterioles were normal. There were slight valvular lesions suggesting rheumatic disease, but the distribution and extent of the scarring were not suggestive of old rheumatic myocarditis. The most plausible view would be that the scarring was the result of an old, acute myocarditis. The other lesions in the case were of subordinate interest.

Anatomic Diagnosis.—Cardiac hypertrophy and dilatation; fibrosis of myocardium; thrombus in ventricle, right; infarcts of lungs; chronic passive congestion of viscera; lobular pneumonia.

CLINICAL FEATURES

There were eight males and two females, ranging in age, at death, from 29 to 66 years. Six were white and four were Negroes. The duration of symptoms from onset to death ranged from ten days to

five years, but eight of the patients lived only eight months after the onset of discomfort. There were no specific antecedent infections common to the group. Two patients were markedly alcoholic; these were male Negroes with positive Wassermann reactions. There were no apparent dietary deficiencies and signs of avitaminosis were not noted.

In each case the symptoms were those of myocardial insufficiency. Various types of arrhythmia were commonly observed; paroxysms of tachycardia occurred in two cases. Abdominal pain was a complaint in three. Cardiac pain of the anginal type was conspicuous by its absence; mild substernal discomfort was mentioned by two patients.

The heart sounds were weak, and gallop rhythm was frequently present. There were no murmurs of valvular disease. The blood pressure was normal or low, save for occasional slight transient elevations during the acute phases of cardiac failure. The Wassermann reaction of the blood was negative in seven, positive in two, and not known in one.

Electrocardiograms were taken in seven cases; three patients died in the first twenty-four hours after admission to the hospital, and a tracing was not made. All of the records showed deviations from the normal; the changes varied according to the extent of the lesions in the heart. In the cases in which there was no fibrosis the changes were slight; in the presence of advanced fibrosis they were extreme. Actively progressive myocardial damage was reflected in the altering form of the complexes and in many types of irregularity. These included inversion of T in Lead I, or in Leads I and II; low voltage; premature beats; auricular fibrillation, both paroxysmal and permanent; paroxysmal auricular flutter; paroxysms of tachycardia originating in the auricles, junctional tissues, or ventricles; and partial and complete A-V block. In three cases bundle branch block developed in the course of the illness and persisted until death.

A noteworthy feature was the occurrence of embolism, arising apparently from mural thrombi in the heart. Infarction of the lungs occurred six times, of the kidneys, four times, and of the spleen, once. In one case there was embolic occlusion of the central artery of the retina.

Death took place as the result of gradually progressive, often recurring, cardiac insufficiency in seven patients; three died suddenly.

In only three of our cases was the correct diagnosis made prior to the autopsy, and this was done by a process of exclusion. The condition which most frequently gave rise to confusion was arteriosclerotic heart disease, in which the signs of coronary insufficiency were not manifest and the true nature of the basic disturbance was apparent only at the post-mortem table. On occasion, instances of coronary thrombosis and atypical rheumatic carditis were regarded as examples of this syndrome until direct examination of the heart was made.

A consideration of etiology is unprofitable because facts are lacking, but a brief reference to the possible role of dietary deficiency is pertinent because of current interest in this field. No signs of a lack of vitamin B_1 were observed, and polyneuritis was notably absent. It is rare to see an advanced degree of beriberi heart disease without involvement of the peripheral nerves. Vitamin therapy was not tried in our patients, yet there were remissions, for which slight modifications in dietary habits could hardly be held accountable. One of von Bonstorff's patients failed to improve after receiving large doses of crystalline thiamine.

Myocardial lesions, consisting of necrosis of the muscle fibers, followed by scarring, have been produced in rats and hogs by a diet markedly deficient in potassium.[17, 18] A relationship between these experimentally induced lesions and similar changes in human hearts has not been demonstrated.

PATHOLOGY

There are several features common to these ten cases. The first is the absence of advanced sclerosis of the coronary arteries. In some of the cases these arteries were normal, whereas, in the remainder, only sclerosis of mild degree was present. In none were the lumina of the arteries compromised, nor was there any calcification or thrombus formation. The orifices of the arteries were not narrowed. Rarely was there any thickening of the intima of the coronary arterioles, and, when this was present, it did not involve the intima of the entire circumference at any one level, but was localized to a small segment, and only slightly reduced the lumen of the arteriole. These mild changes in the arteries and arterioles were too insignificant to be held responsible for any lesions found in the myocardium.

It may be added that in no single case was there generalized arteriolar sclerosis. Such atherosclerosis of the aorta as was present was not of marked degree and, indeed, in many of the cases, it was less than might reasonably have been anticipated from the ages of the patients. Furthermore, in those cases in which the blood showed a positive Wassermann reaction, anatomic evidence of syphilis was entirely lacking.

Another feature was the hypertrophy of the myocardium that, although variable in degree, existed in each case. The myocardial fibers showed the usual evidences of hypertrophy, namely, increased size, with enlargement, hyperchromatism, and altered shape of the nuclei.

In Cases 1, 2, 3, and 4, examination revealed only hypertrophy of the myocardium without any scarring, either gross or histologic. A careful review of all of the lesions found in these cases at autopsy does not disclose any that could be held accountable for the cardiac hypertrophy.

An insignificant increase of stroma in the myocardium was found in two cases (5 and 6). This was laid down between the myocardial fibers and did not replace any of them. It would seem most unlikely that this could in any way have been responsible for the hypertrophy; indeed, it is more probable that this increased supporting tissue between the myocardial fibers was secondary to the hypertrophy, as is so often the case.

More extensive lesions were present in the hearts from Cases 7, 8, 9, and 10. In the first two cases of this group (7 and 8) the myocardium had undergone recent necrosis. The appearance and distribution of the necrotic areas in the first of these two (7) suggested infarction, although no cause for this was found. The necrotic muscle impinged on the conduction bundle branches.

In the second of these two cases (8) the necrosis was very widespread; it was found in the walls of both ventricles and in the interventricular septum. It was very evident that in all of these situations the conduction fibers were frequently involved. Areas of scarring indicated the sites of previous necroses, and these resulting scars appeared to be of different ages, for some were compact and others looser in texture. Near the arterioles, in the neighborhood of the necrosis and scars, small aggregates of lymphocytes were gathered. These cell accumulations were not regarded as evidence of syphilis, but as part of the reaction to the necrosis. The history, the negative Wassermann reaction, and the absence of any anatomic evidence of syphilis oppose the possibility that the cardiac lesions could have been of syphilitic origin.

The two remaining cases (9 and 10) are examples of extensive scarring without any demonstrable cause, both occurring in patients with positive Wassermann reactions. Over quite large areas the cardiac muscle had been replaced by compact scars. In one of these cases (9), sparse perivascular accumulations of lymphocytes were found near the scars; these were interpreted as secondary to the myocardial damage and not as indicative of the etiology of the lesion. Careful study of the various viscera did not reveal any evidence of syphilis, and the myocardial changes were not believed to be syphilitic.

In the other of these two cases (10) there were large myocardial scars without any perivascular lymphocyte collections. Here also, although the Wassermann reaction was positive, there was complete absence of any lesions in other organs that could be interpreted as syphilitic, and it does not seem plausible that the myocardial scars were due to a previous syphilitic myocarditis.

The scarring in Cases 9 and 10 might conceivably have resulted from necroses similar to those described in Case 8, although no suggestion can be made as to what produced the lesions in these three hearts, for the common causes would seem to have been completely eliminated.

The lesions were not the same as those that have been described in syphilitic myocarditis.

Thrombi were found in six of the ten hearts, twice in the right auricle, twice in the right ventricle, and four times in the left ventricle. Histologic studies of the myocardium and endocardium beneath the thrombi gave no clue as to what initiated the formation of the thrombi. The endocardium beneath the thrombi was either normal or, when abnormal, the changes were clearly related to the process of organization of the thrombi. The myocardium was hypertrophied but not scarred or necrotic immediately beneath the thrombi. As might have been expected, these thrombi were the sources of emboli, and infarcts were discovered in the lungs in each case, in the kidneys in four, and in the spleen in one.

Finally, it may be noted that there were no valvular lesions that could have played a role in the production of the hypertrophy. There were five instances in which the mitral leaflets were altered, and in these the lesion was not sufficient to have disturbed the competent closure of the valve cusps. The same was true in those cases in which the aortic cusps were thickened at their bases.

There was only one instance of pericardial adhesion (Case 2). The adhesion covered only a small area of the posterior surface of the heart, and it is most unlikely that it could have exerted any effect that would have resulted in the hypertrophy.

SUMMARY

These cases appear to form a clinical group of which the chief features are: marked cardiac hypertrophy; symptoms of cardiac insufficiency; occurrence of various types of arrhythmia; frequent emboli to the pulmonary and systemic circulations; rapidly progressive course after the onset of symptoms; and death from gradual cardiac failure or in sudden fashion. The cause of the syndrome is unknown.

The hearts, at autopsy, all show hypertrophy of the muscle fibers. In some cases, this is the only lesion. In others there is also fibrosis, which, in different instances, may be slight or extensive. There may be areas of necrosis, both old and recent. Intracardiac thrombi are often present.

Whether these cases represent a single disease picture, observed at different stages of its development, or are to be regarded as of heterogeneous origin, cannot now be stated. Only a knowledge of the etiology can furnish an answer to this question.

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UNUSUAL CONDITIONS INVOLVING THE ABDOMINAL AORTA

Seven Cases With Autopsy Observations

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VARIOUS diseases of the abdominal aorta are associated during their course with dramatic symptoms. They are also of unusual interest because of their rarity and difficulty of diagnosis. We have been fortunate in accumulating seven cases of unusual conditions involving the abdominal aorta, with autopsy observations. These include mycotic aneurysm and involvement by tuberculosis and malignant tumors.

I. MYCOTIC ANEURYSM

The following are two very similar cases of rupture of the abdominal aorta due to a rare and unusual etiological factor. An ante-mortem diagnosis was made in one of the cases.

Case 1.—J. C., a 30-year-old Italian printer, was admitted with a chief complaint of swelling of his joints for three weeks. One month previously, he had a streptococcus sore throat. The next day his left knee became swollen, and this was followed by right ankle and knee involvement in a few days. He was given three different sulfonamide derivatives with some remission. During the last few days before admission the symptoms recurred and he was hospitalized. He had had pneumonia complicated by rheumatic fever six years before.

Examination.—Examination revealed a well-developed man who did not appear acutely ill. The fundi were negative. The pharynx was slightly reddened, but there was no cervical lymphadenopathy. The heart was of normal size and regular. The blood pressure was 120/80. There were soft systolic apical and basal murmurs. There was fluid in both knee joints, with a floating patella on the left. The left ankle was reddened, hot, and swollen. The clinical impression was acute rheumatic fever.

Course.—On salicylates, the temperature fell in two days from 101° to 99° F., but rose two days later to 104° F., where it remained until the end. Although the pulse rate and sedimentation rate were still rapid, the joint swelling and heart murmurs improved. On the third day, severe pain appeared over the left sacroiliac joint, with tenderness but no swelling. On the seventh day he developed numbness down the left thigh and leg, with absent knee jerk and definite muscle weakness. All other sensations and reflexes were unimpaired except for hyperesthesia from the second lumbar spine downward. The clinical impression was psoas abscess. Blood cell counts at this time revealed a moderate secondary anemia and 28,350 leucocytes, with 95

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Received for publication Jan. 3, 1944.

per cent polymorphonuclear neutrophiles. On the ninth day he developed a friction rub over the left anterior axillary line, with occasional crackling râles. Fullness appeared in the left flank which was described on the tenth day as a small, tender, hard mass in the left lumbar region. On the twelfth hospital day a nonfading, petechial macular eruption appeared over the lower abdomen and extremities. They measured 1 to 5 mm. in diameter. Paralysis of the left lower extremity became complete. He developed an unrelieved hiccup. On the seventeenth hospital day, marked scleral jaundice appeared, but the liver and spleen were not palpated. The van den Bergh reaction was direct, the icteric index, 42, and the serum bilirubin, 4.5 mg. per 100 c.c. of blood. A blood culture at this time revealed *Streptococcus hemolyticus*. Two subsequent cultures corroborated this finding. The heart became enlarged to the anterior axillary line, and there were a double murmur at the apex and a soft systolic murmur at the pulmonic area. On the eighteenth hospital day, bilateral basal râles appeared, with fluid at the left base. A pericardial friction rub was heard to the left of the sternum. The firm tender mass in the left flank became very pronounced, and transmitted an impulse. On the twentieth day all joints became painful, especially the left wrist and elbow. Purulent material from the elbow yielded a culture of *Str. hemolyticus*. Diarrhea became pronounced, but stool culture was negative for the typhoid-dysentery groups. Thoracentesis on the twenty-fourth day revealed a hemorrhagic fluid, and Type VI pneumococcus was identified. The mass in the flank became markedly pulsating, transmitting a harsh systolic sound which radiated to the left. The patient became stuporous and died on the twenty-ninth day. The final diagnosis was mycotic aneurysm of the aorta, with possible dissection along its major branches and into the left subphrenic area retroperitoneally, with formation of a hematoma or abscess anterior to the left psoas muscle.

Further Studies.—The electrocardiogram showed left axis deviation. The transverse diameter of the heart was enlarged as would be expected with rheumatic mitral valvular disease. No osseous changes were noted in the left knee, ankle, or pelvis. The psoas muscle on the left was obscured by a shadow, with evidence of a soft tissue density at the lower portion of the left kidney suggestive of a mass or collection in the left retroperitoneal space. In the pyelograms, the medial outline of the left kidney appeared indistinct, and no dye excretion was visualized on this side. The blood and spinal fluid Wassermann reactions were negative. The blood uric acid, urea, sugar, and creatinine were 2.7, 29, 84, and 1.2 mg., respectively, per 100 cubic centimeters. Terminally, the urea and creatinine rose to 105 and 2.14 mg. respectively, per 100 c.c. of blood. The temperature ranged between 101° and 104° F.

Autopsy.—Autopsy revealed 250 c.c. of clear yellow fluid in the peritoneal cavity. The sternoclavicular joints and left knee contained pink, purulent fluid. Behind the manubrium was an abscess cavity, 3 cm. in diameter. There were seven small abscesses under the epicardium, but the heart itself was entirely negative. A large, firm, retroperitoneal mass protruded into the peritoneal cavity from the second to the fifth lumbar vertebrae, extending from the left flank to just beyond the right vertebral borders. About 5 cm. above the aortic bifurcation, the wall was necrotic and ruptured. It connected with the large sac containing friable tissue mixed with blood clots. Microscopically, the blood clots were degenerated without attempt at or-

ganization, and incorporated an occasional colony of hemolytic streptococci. There was slight atherosclerosis of the abdominal aorta, with extensive suppurative necrosis and an abscess in the adjacent tissue. In addition, there were hemorrhagic infarcts of the lung, kidneys, and spleen.

Final Diagnosis.—The final diagnosis was septicemia (blood cultures positive for *Str. hemolyticus*), with suppurative arthritis as the primary focus. This resulted in mycotic aneurysm of the abdominal aorta, with rupture; septic infarcts of the lungs, spleen, and kidneys; and suppurative myocarditis and abscess of the mediastinum.

CASE 2.—R. H. (case of Dr. H. Wolfer), a white man, aged 42 years, was admitted with pain in the hands of three weeks' duration. Three weeks previously he had developed pain and swelling in all the joints of the left arm. The right arm became similarly involved, and then the lower extremities, but these symptoms gradually disappeared except for a slight residuum in the right hand and knee and left shoulder. Twenty years before, he had had migrating joint pains which cleared up spontaneously.

Examination.—Examination revealed a well-developed man who appeared acutely ill. Except for a cataract on the left side, the head was negative. The neck, lungs, and heart were entirely negative. The blood pressure was 125/65. The right knee and hand and left shoulder and ankle were red, swollen, and tender. The temperature was 104° F. The diagnosis was acute infectious polyarthritis.

Laboratory Data.—These included a leucocyte count of 17,800, with 85 per cent polymorphonuclears; this rose to 22,700 four days later. Urinalysis, and the gonococcus fixation and Wassermann reaction were negative. The blood urea and uric acid were 40 and 3.6 mg. per 100 c.c. of blood, respectively. Roentgenograms revealed soft tissue swelling, and slight irregularity of the right radiocarpal joint.

Course.—The temperature continued to be 104° F. Three days after admission he developed thrombophlebitis of the left leg, with swelling and edema. There were also tenderness, spasticity, and fullness in the left flank which were thought to be due to a perinephric abscess. Excretion pyelograms revealed outward displacement of the left kidney by a markedly prominent psoas shadow; this was suggestive of a perinephric abscess. Retroperitoneal exploration revealed inflammatory adhesions and induration, with very little pus. Many fresh clots were encountered, and their removal resulted in a massive hemorrhage. Microscopic examination revealed only old and fresh blood clots containing clumps of short-chained cocci and diplococci. Despite three blood transfusions, the patient became comatose, and developed massive fatal pulmonary edema two days after operation.

Autopsy.—Autopsy revealed a normal heart which weighed 300 grams. There was bilateral bronchopneumonia, but no evidence of thrombosis or embolism. The aorta showed very slight atheromatous plaque formation throughout. Two inches above the bifurcation of the aorta there was an aneurysmal opening posteriorly, measuring 2 by 1 cm., with well-rounded edges. This led to the left into a large mass of fibrin and blood clots which infiltrated the iliopsoas, quadratus lumborum, and oblique and transversalis muscles posteriorly. This measured 6 cm. in circumference. No pus or arterial occlusion was noted. The left femoral vein below the inguinal ligament was occluded by a firm thrombus. A small thrombus was also found halfway up the

inferior vena cava. The kidneys were essentially negative except for an infarct measuring 1.5 cm. in the left renal cortex.

Microscopic examination of the aorta revealed slight atheromatous ulceration of the intima, with focal lymphocytic and fibroblastic proliferation of the intima and media. Sections through the area of rupture consisted of partly organized clot containing erythrocytes and polymorphonuclear cells, fibrin, and abundant bacterial colonies. Much necrosis was present throughout. Special elastic tissue stains revealed some splitting of the internal elastic lamina and moderate to marked thinning of the medial elastic tissue. The adventitia contained only a few scattered elastic fibers. The femoral vein contained a septic thrombus, with marked perivascular lymphocytic infiltration of the media and adventitia.

Final Diagnosis.—The final diagnosis was mycotic aneurysm of the abdominal aorta, with necrosis, rupture, and retroperitoneal hemorrhage; acute inflammatory reaction of thrombotic extravasated blood; septicemia; thrombophlebitis of the left femoral vein; bronchopneumonia; focal necrosis of the liver; and septic infarct of the left kidney.

Comment.—These cases are similar in that both occurred in young white men with a previous history of joint pains. Each entered with a chief complaint of joint pains, had a fever up to 104° F. and a leucocyte count over 20,000, with neutrophilia, and had *Str. hemolyticus* bacteriemia. No cardiac disease was found in either case, despite rheumatic histories. Septic infarctions were found in both cases, involving the kidney in one, and the kidney, lung, and spleen in the other. Both had swelling in the lumbar region which proved to be mycotic aneurysms with masses of clotted blood infected with *Str. hemolyticus.* The sequence of events in both cases was initiated by septic arthritis with septicemia. The blood stream then carried the organisms to the vasa vasorum, with resultant infectious aortitis and medial necrosis.[1] Intimal tears terminated in rupture of the mycotic aneurysms.

II. TUBERCULOSIS AND ANEURYSMS

It is the present concept that tuberculosis cannot involve the aorta unless the lungs are diseased, thereby limiting the process to the thoracic segment. Dafoe[3] found only eleven cases of aortic aneurysm due to tuberculosis, with rupture in two of the cases. He added two reports to the literature. Kornitzer[4] described a tuberculous dissecting aneurysm of the ascending aorta in a young boy with miliary tuberculosis. Schmorl[5] found five cases out of 123 autopsies on patients with acute miliary tuberculosis in which tubercle bacilli had invaded the atheromatous ulcers. The bacilli may infect the media or adventitia through the vasa vasorum. Finally, there may be direct extension from a near-by focus, such as an infected lymph node or abscess.

The process is rapidly progressive in the larger blood vessels and aorta because fibrous tissue proliferation is not so marked as in the smaller arteries, with a tendency to aneurysmal formation. The proc-

ess consists of the usual infiltration by lymphocytes and endothelial and giant cells, with caseation.

Two unusual cases are presented to illustrate the possible influence of tuberculosis as a factor in the production of saccular aneurysm of the abdominal aorta through the activity of tuberculous cold abscesses.

CASE 1.—J. F. (case of Dr. C. H. Greene), a white man, aged 50 years, was admitted with pain in the abdomen extending into the flanks and back. It was not localized, but became severe after walking. Three months previously, he suffered from pneumonia, followed by empyema.

Examination.—Examination revealed bilateral basal râles. The blood pressure was 150/90. There was tenderness in the epigastrium, and the liver extended three fingerbreaths below the costal margin. A month later he developed pains along the left leg, associated with herpetic lesions. A pulsating mass the size of an orange, with a systolic thrill and bruit, was first recognized in the abdomen. Absence of the dorsalis pedis pulsations was noted, with positive Babinski reflexes. A diagnosis was made of aneurysm of the abdominal aorta. Early gangrene of the left foot was noticed the following day. The blood pressure in the upper extremities was 140/100, but it was 70/0 in the right leg. This was thought to be due to the development of a saddle thrombus. Operation was inadvisable because of poor response to therapeutic measures. The patient failed rapidly, and died two months after admission.

Laboratory studies.—These studies included a normal electrocardiogram. Roentgenograms revealed an increase in the sweep of the second and third portions of the duodenum due to a mass or enlargement of the head of the pancreas. Both kidneys were in their normal positions. There was no evidence of paraspinal or psoas disease. Retrograde pyelograms revealed inadequate filling of the lower left renal calyces. The blood urea, creatinine, and sugar were 21, 1.1, and 84 mg. per 100 c.c., respectively. The blood Wassermann reaction was negative. The galactose tolerance test was normal. There was no free hydrochloric acid in the stomach, and the total acidity was 20 degrees. The icteric index was 19, and there was 0.55 mg. of bilirubin per 100 c.c. of serum. Repeated urinalysis revealed a trace of albumin and a few epithelial cells, erythrocytes, and leucocytes. The leucocyte count was 25,000, with 88 per cent polymorphonuclears. The temperature was normal throughout except for a terminal rise to 101° F.

Autopsy.—Autopsy revealed a glistening, blue-black discoloration of all the toes of the left foot, extending midway up the tarsus. The heart was entirely normal. The aorta presented numerous, irregularly scattered, atheromatous plaques, with an average diameter of 4 millimeters. Just below the head of the pancreas there was a fusiform sac which was fluctuant on pressure and was situated directly over the spinal column, extending 2 inches anteriorly and covering the second to the fourth lumbar vertebrae. The mass contained thick, creamy, purulent material, from which a culture was subsequently reported as positive for tubercle bacilli. Careful dissection revealed a saccular aneurysm of the abdominal aorta, measuring 2 inches in diameter. Immediately posterior to the aneurysm there was a cold abscess. Examination of the vertebrae revealed no evidence of tuberculous involvement. At the bifurcation of the inferior vena cava there was a recent

saddle thrombus extending into the iliac vessels for 3 inches. The right kidney weighed 195 grams, the left, 250 grams. The capsules were stripped with difficulty, exposing an irregular, pitted surface. The cortex was of uneven thickness, with distortion of the pyramids. On microscopic examination there was evidence of chronic pyonephritis and chronic interstitial nephritis. The aorta presented moderate atheromatous degeneration. The lungs showed bronchopneumonic consolidation, but no evidence of tuberculosis.

Final diagnosis.—The final diagnosis was saccular, arteriosclerotic aneurysm of the abdominal aorta, tuberculous cold abscess (retroperitoneal), gangrene of the left foot, saddle thrombus of the inferior vena cava, and bilateral bronchopneumonia.

CASE 2.—H. S. (case of Dr. J. H. Cawford), a white man, aged 64 years, was admitted with a history of having lost his balance after drinking, and falling on his right knee. He had had a hemorrhoidectomy three months previously. For three weeks he had had chills, fever, and a productive cough, but no dyspnea, hemoptysis, or pain in the chest. He had had occasional nausea and abdominal pain.

Examination.—Examination revealed a complete transverse fracture of the right patella. The heart was not enlarged; it was regular and there were no murmurs. The blood pressure was 144/80. The lungs showed medium moist râles and dullness at the right base posteriorly. The diagnosis was hypertensive arteriosclerotic heart disease and early bronchopneumonia.

Course.—The bronchopneumonia of the right lower lobe became more confluent and progressive, with a temperature rise to 104° F. Because of the development of a maculopapular eruption and persistence of the fever, sulfathiazole therapy was discontinued. He began to develop congestive heart failure, and digitalis therapy was instituted. His pneumonia subsided one week later, but became low grade in nature, with persistent moist râles at the bases, more marked on the right. Three weeks after admission, he suddenly developed an acute attack of dyspnea and cyanosis. Auricular fibrillation, poor heart tones, and a systolic murmur at the apex were noted. The clinical impression was pulmonary infarction. He died two hours later.

Laboratory studies.—These studies included electrocardiograms which showed complete heart block, left axis deviation, and a digitalis effect. Roentgenograms of the chest revealed bilateral bronchopneumonia, arteriosclerotic configuration of the heart, and atherosclerosis of the aortic arch. The blood culture and Wassermann reactions were negative. The blood sugar, urea, and creatinine were repeatedly normal. The leucocyte count was 10,450, with 85 per cent polynuclears. Urinalysis was slightly positive for albumin.

Autopsy.—Autopsy revealed bilateral apical adhesions, with a tuberculous cavity in the left apex measuring one inch in diameter. This contained caseous material. In the superior margin there was a single calcified nodule. The remainder of the lung showed edema and engorgement, with basal bronchopneumonia. The heart weighed 450 grams, and was the seat of coronary artery sclerosis, myocardial fibrosis, and hypertrophy of the left ventricle. The aorta was involved by numerous atheromatous plaques and hemorrhagic necrosis. One inch inferior to the right renal artery there was a saccular aneurysm 2 inches in diameter. The aneurysm was in close contact with an abscess

over the right psoas muscle. This contained 25 c.c. of light-gray, purulent material. Cultures revealed tubercle bacilli.

Microscopic examination.—This included sections of all organs, and corroborated the gross observations. Sections taken through the aneurysm revealed marked irregular intimal thickening due to hyperplastic arteriosclerosis. The media showed moderate calcification. The adventitia was uninvolved.

Final diagnosis.—The final diagnosis was saccular arteriorsclerotic aneurysm of the abdominal aorta, tuberculous cold abscess of the left apex, bilateral bronchopneumonia, arteriosclerotic and hypertensive heart disease, chronic passive congestion of all organs, and fracture of the right patella.

Comment.—These cases present certain striking similarities. They occurred in men in the fifth and sixth decades of life. There proved to be an underlying, advanced, atheromatous degeneration of the abdominal aorta. Further weakening of the wall, with aneurysm formation, probably resulted from the adjoining cold abscesses, both of which proved to be tuberculous. The fact that the masses in both cases were in the closest proximity strengthens this belief. No primary focus was recognized clinically in either case. In the first case, although the lungs and vertebrae were clear, tubercle bacilli were later demonstrated in the abscess. In the second, the focus might possibly have been the tuberculous pulmonary cavity. Another point of interest was the occurrence of gangrene of the left foot due to saddle thrombus formation. Although clinically it was placed at the bifurcation of the aorta,[2] at autopsy it proved to be at the bifurcation of the inferior vena cava.

III. MALIGNANT TUMORS AND THE AORTA

Although the aorta is susceptible to degenerative and inflammatory diseases, this highly elastic, pulsating vessel is notoriously resistant to invasion by malignant tumors. In view of their rarity and the different types of tumor involved, it was deemed worth while to report the following three cases. In the first two cases, death was caused by sudden rupture of the aorta into the esophagus; in the third case, death was precipitated by infection secondary to a reticulum cell sarcoma, with resultant saddle thrombus. Infection was a secondary factor in Cases 1 and 2, although more advanced in the latter.

CASE 1.—J. S., a white man, aged 50 years, a bricklayer, was admitted complaining of inability to swallow solid food and vomiting, accompanied by substernal pain of eight months' duration. The onset of symptoms was preceded by a cold which caused him to wheeze and spit up blood-flecked sputum on several occasions. There had been a loss of 30 pounds since the illness commenced, probably because he limited himself to a liquid diet. He had been a heavy drinker until eighteen months prior to admission.

Examination.—Examination revealed an emaciated man with wheezing respiration. The heart was in the sixth intercostal space just out-

side the midclavicular line. No murmurs were heard and the heart tones were of good quality. The blood pressure was 146/98. No metastases were found.

Laboratory studies.—These studies included an esophagram which showed a constant irregularity at the junction of the upper and middle thirds, about 2 inches in length, with slight obstruction above this point. Esophagoscopic examination revealed, at a depth of 28 cm., a fungating, easily bleeding mass, mainly on the posterior wall, but completely encircling the esophagus. It appeared to be submucosal both anteriorly and laterally, with considerable constriction. Biopsy of the esophageal mass revealed a typical epidermoid carcinoma. The blood urea, creatinine, and sugar were normal, and the Wassermann reaction was negative.

Course.—A Witzel type of gastrostomy was performed, and no metastases were found. This was done preparatory to resection of the neoplasm, with establishment of a tube graft to the upper part of the esophagus. Three weeks later, while the patient was on a bed pan, a gush of bright red blood appeared in his mouth. He fainted, and died shortly thereafter.

Autopsy.—Autopsy revealed a necrotic, ulcerated carcinoma involving the midportion of the esophagus and measuring 6 inches in length. The ulceration, about the thickness of a finger, was noted immediately beneath the posterior portion of the aorta. Opening the aorta in this region revealed two pin-point openings, surrounded by a zone of hyperemia. Pressure on the ulcerated mass caused fluid to exude into the aorta. The carcinomatous mass was firmly attached to the aortic adventitia 2 inches below the descending aorta. The aorta showed occasional, irregular, raised, subintimal, atheromatous plaques. The gastrostomy wound and the entire stomach wall were well healed. However, the stomach was distended by 1,000 c.c. of clotted blood. There was a small pulmonary abscess in the upper portion of the left lower lobe.

Microscopic examination of the esophagus confirmed the diagnosis of epidermoid carcinoma, with periesophageal necrosis and suppuration. Sections of the aorta showed the carcinoma invading the adventitia, with periaortic suppurative inflammation, necrosis, and hemorrhage. No other metastases or involvement were noted after extensive microscopic studies.

CASE 2.—P. B., a 58-year-old unemployed white man, was admitted because of bleeding from a gastrostomy wound and hematemesis which followed his supper. About eighteen months previously he had developed dysphagia, regurgitation (first solids, later liquids), and weight loss. Gastrostomy was performed at the Memorial Hospital. Three weeks earlier he had been admitted because of a similar hemorrhage. The past and family histories were noncontributory.

Examination.—Examination revealed a pale, emaciated man who was regurgitating small amounts of bright red blood. Blood was exuding from the opening in the left side of the epigastrium. There were no lymph node enlargements or metastases. The blood pressure was 86/60, and the heart, lung, and abdominal examination was negative. He continued to bleed profusely and died twenty hours after admission.

Autopsy.—Autopsy revealed an epidermoid carcinoma of the esophagus which had eroded into the aorta at the level of the tracheal bifurcation. Death resulted from a split-pea-sized rupture of the aorta,

rather than bleeding from the malignancy itself. The carcinoma did not invade the trachea or regional lymph nodes, but was firmly attached to the adventitia of the adjacent aorta.

CASE 3.—H. T. (case of Dr. B. Fedde), a white female houseworker, aged 39 years, was admitted with a history of pain of a girdle nature around the abdomen and in the lower extremities. There was also weakness of the legs. She was irrational and confused.

Examination.—Examination revealed paralysis of both lower extremities, with flaccidity and bilateral foot drop. All reflexes and sensations were absent in the legs. There were muscle tenderness and pain on passive motion of the legs. The right leg was very cold below the knee, and the left was cold below midleg. Later this extended to about mid-thigh in an irregular manner. The dorsalis pedis artery pulsations were not palpable. Neurosurgical consultation by Dr. J. Browder, three days later, led to a diagnosis of occlusion of the abdominal aorta at the iliac bifurcation, but it was then too late to intervene. The patient died six days later because of the increasing extent of the gangrene.

Laboratory studies.—These studies revealed a normal spinal fluid, no nitrogen retention in the blood, and a negative Wassermann reaction. The leucocyte count rose from 38,900 to 66,300 (with 81 per cent polynuclears) in three days. Roentgenologic examination suggested the presence of a left iliopsoas mass. The temperature ranged from 98° to 99.8° F.

Autopsy.—The heart weighed 520 grams and contained no thrombi or vegetations. Situated at the bifurcation of the aorta was a saddle thrombus extending 1¼ inches upward into the aorta, 2 inches into the right common iliac artery, and 1 inch into the left common iliac artery; both iliac arteries were completely occluded. The thrombus was well organized, gray white, and very adherent to the intima. There was a bilateral abscess over the lower fourth of the psoas muscles. A small tumor overlying the fifth lumbar vertebra proved to be a reticulum cell sarcoma which invaded this vertebra, with secondary abscess formation. Other sections of the aorta showed myxomatous degeneration of the intima and media, with organizing adherent thrombi. In the periaortic tissues there was septic thrombosis of the capillaries.

Comment.—The sequence of events in this case began with a small, reticulum-cell sarcoma which invaded the area about the fifth lumbar vertebra in close proximity to the aorta. Resultant infection, with the formation of bilateral psoas abscesses, produced the additional factors of infection and pressure upon the aorta. However, before the process could invade far enough to produce actual rupture, a saddle thrombus formed[2] and caused complete occlusion.

SUMMARY

1. Two strikingly similar cases of mycotic aneurysm of the abdominal aorta, with rupture, are reported. The primary focus in both was septic arthritis caused by the *Str. hemolyticus*. The diagnosis was made ante mortem in one of the cases.

2. Two rare cases of saccular aneurysms of the abdominal aorta, due to atheromatous degeneration in association with tuberculous cold abscesses, are presented.

3. Three cases of malignant tumor of contiguous structures affecting the aorta are described. In two similar cases, the process was an epidermoid carcinoma of the esophagus; in the third, it was a reticulum-cell sarcoma. Secondary infection occurred in both cases and was the immediate cause of death in the third case.

I am indebted to Dr. William Hala and Dr. C. Burn for the pathologic studies.

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EFFECTS OF EMETINE ON THE ELECTROCARDIOGRAM

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EMETINE hydrochloride has been used in the treatment of amoebic dysentery since Rogers[1, 2] advocated it in 1912. Levy and Rowntree,[3] in 1916, called attention to the dangerous effects of large amounts of emetine on the circulatory system, and supported their contention with experimental animal work. Goetz[4] reported on the therapeutic effects and dangers of emetine at the Medical Association of the Isthmian Canal Zone in 1936. Since that time the electrocardiograph has been used at the Gorgas Hospital to aid in the evaluation of the condition of the heart while the patient is under emetine therapy. Recently, Boyd and Scherf[5] used experimental animals to study the effects of acute emetine intoxication. They found, among other changes, widening of the ventricular complex, which was accompanied by cardiac dilatation. Auriculoventricular conduction time changes were noted. They found that the T wave tended to assume a reciprocal relationship to the initial deflection. Auricular extrasystoles and auricular tachycardias were the most common arrhythmias. Advanced stages of intoxication were required for the production of ventricular extrasystoles. Chopra and Sen[6] reported S-T depression in a case of emetine intoxication, although Boyd and Scherf did not think that this was due to emetine.

We have reviewed a number of the charts of patients who received emetine treatment for amoebic dysentery at the Gorgas Hospital. Those who were ill with other diseases which might affect the electrocardiogram were eliminated. This series is composed of seventy-two cases, in all of which electrocardiograms were taken before, during, and at the end of the emetine treatment. A number of the patients had additional records which were taken during or after the therapeutic course. The routine therapy consisted of one-half grain of emetine hydrochloride subcutaneously twice a day for ten days. Emetine by mouth was not used in this study.

Changes were noted in all limb leads equally, and were less common in Lead IVF. Q-wave changes were not found. Thirty-eight, or 52.7 per cent of the series, showed changes. Thirty-three of these, or 45.8 per cent of the total of seventy-two, had depression of the T waves varying from slight lowering of the amplitude to complete inversion. Ten of these showed inversion in one or more leads. The auriculoventricular conduction time was increased in seven instances (9.7 per cent), but in only one case did it become abnormal. This

From the Medical Service, Gorgas Hospital, Ancon, Canal Zone.
Received for publication Dec. 20, 1943.

occurred on the seventh day of the ten-day course; the P-R interval was lengthened to 0.24 second, i.e., first degree A-V heart block. The condition persisted through the tenth day, and then decreased slowly until, on the eighteenth day, the conduction time was 0.20 second (Fig. 1). Only four in the group (5.5 per cent) showed premature systoles. These were both auricular and ventricular, but the ventricular premature systoles predominated. Only one patient had auricular premature systoles and these changed to ventricular with added amounts of emetine. A coronary T wave occurred in one case, and is described in detail.

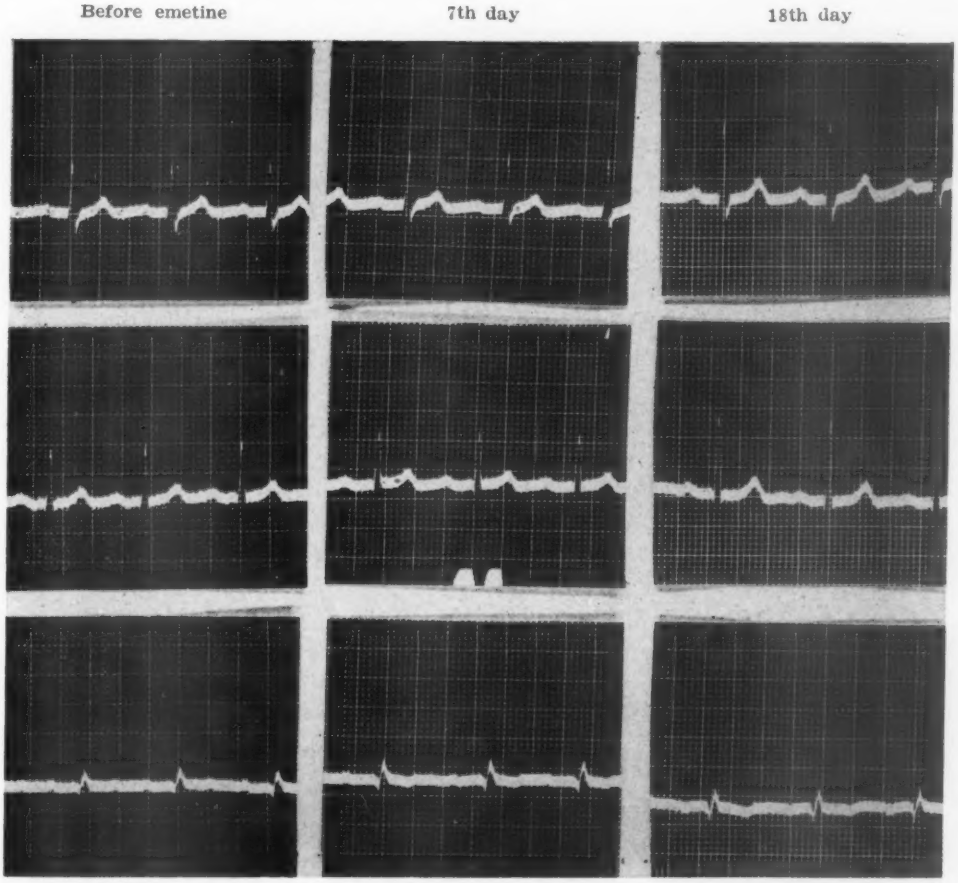

Fig. 1.—The above electrocardiogram shows increased auriculoventricular conduction time following emetine. This was first noted on the seventh day of treatment and persisted through the tenth day, when the drug was discontinued. This was followed by slow return toward normal.

REPORT OF CASES

CASE 1.—In the case of F. R., a native of Costa Rica, 31 years of age, changes in the electrocardiogram were brought about by emetine. These changes were not permanent, but were more than transitory, for they persisted over a period of at least four weeks after the drug had been discontinued (Fig. 2).

He entered the hospital Aug. 28, 1942. Emetine therapy was instituted September 3, and continued for ten days in doses of one-half grain twice a day. An electrocardiogram taken before therapy was normal. Successive tracings were made at intervals until the thirty-fifth day. The only significant changes were in the amplitude of the T waves, as shown in Table I.

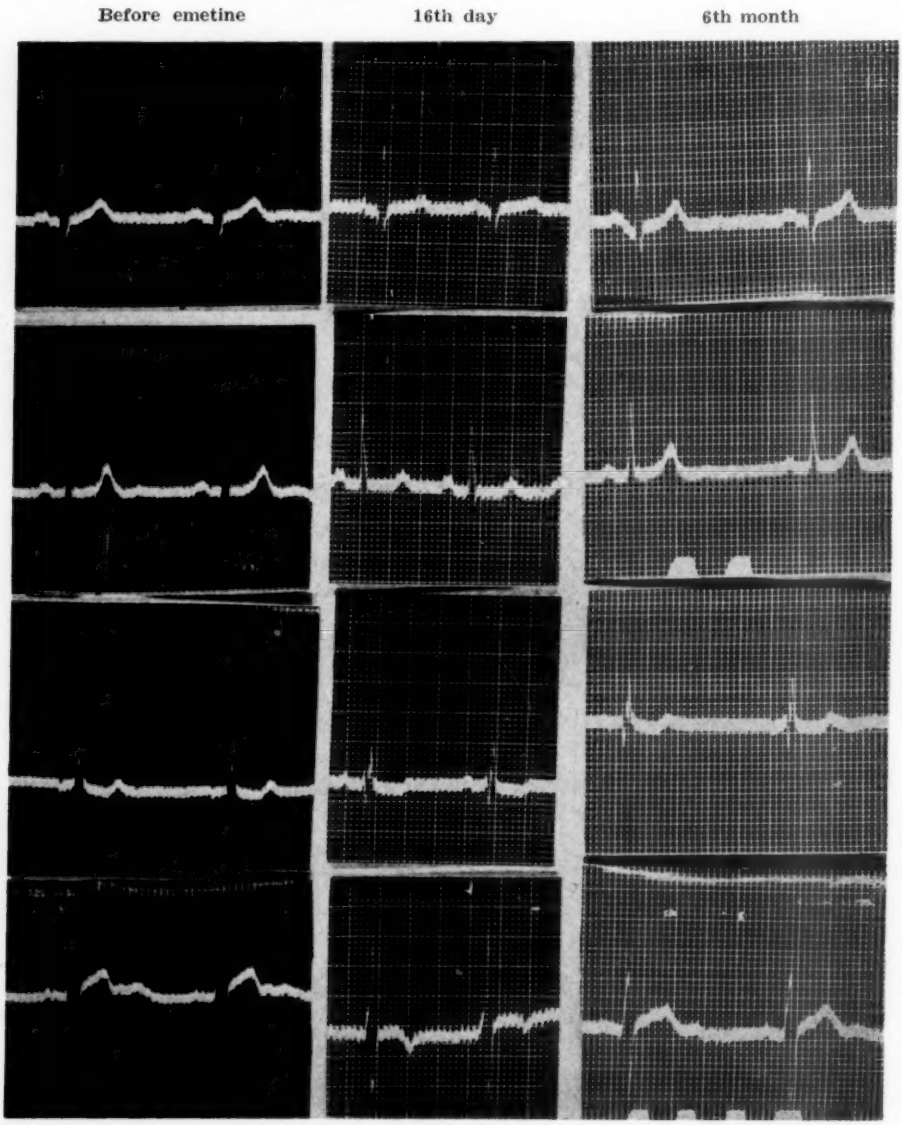

Fig. 2.—Representative electrocardiograms showing the lowering of T waves in the limb leads and inversion of T_4. Followed much later by return to normal (Case 1).

The patient complained of precordial pain on the last day of treatment, when T_4 first showed changes. This pain would come on during rest in bed, and was not severe. It would persist for about an hour.

The sharp feature of the pain continued for ten days, and was then followed by a precordial ache which disappeared after two more weeks.

The probability of myocardial infarction was given consideration in view of the precordial pain and coronary type of T wave in Lead IV. However, there were no changes in the RS-T segments, R_4 persisted, and no Q-wave changes were present. Also, there was no temperature elevation or leucocytosis, and the sedimentation rate remained normal. No friction rub was heard.

The patient was permitted to return to work October 17; he was asymptomatic, but T_4 was still inverted. Instructions were given to report for a recheck in one month, but he did not do this. He was not seen again until March, 1943, when he returned for another cause. The electrocardiogram was normal, with an upright T_4 of 4 millimeters.

Emetine was given subcutaneously to four other patients to note the immediate effect. Electrocardiograms were taken at intervals of five minutes and one-half hour after emetine hydrochloride was injected.

TABLE I

DAY OF MEDICATION	AMPLITUDE OF T WAVES (MM.)				MISCELLANEOUS
	T_1	T_2	T_3	T_4	
0	2.50	3.50	1.50	3	Before emetine
5	2	2.50	1	3	Upright T_4
10	2	1.50	−1.50	Diphasic +2 and −1.50	Last day of medication Onset of pain
16	1	1.50	−0.50	−2	Post emetine
19	0.50	1.50	0.75	−2.50	
23	0.50	1.50	1	−3	
28	1	2	1	−2.50	
35	0.75	2	1	−2.50	Inverted T_4
6 mo.	3.1	4.2	1	4	Upright T_4

TABLE II

TIME OF MEDICATION	SECONDS	AMPLITUDE OF T WAVES (MM.)				MISCELLANEOUS
	A-V INTERVAL	T_1	T_2	T_3	T_4	
0	0.16	1	1.25	0.25	2	Left axis deviation R_4 present
5th day before medication	0.16	0.75	0.50	Slight inversion	0.75	R_4 absent Auricular extrasystoles
5 min. after medication	0.17	0.50	Diphasic +0.25 and −0.50	Slight inversion	0.25	Ventricular extrasystoles Marked sinus arrhythmia
½ hr. after medication	0.17	0.50	Diphasic +0.50 and −0.50	Slight inversion	−0.25	Ventricular extrasystoles

CASE 2.—This experiment was on a 69-year-old Negro who had been receiving emetine for five days. Slight T-wave changes were pre-

sent. Further, slight T-wave depressions occurred, and marked sinus arrhythmia was present immediately after the injection of one-half grain of emetine. This was noted neither before the injection nor one-half hour later. Reference to Table II will show the degree of changes.

Boyd and Scherf[5] produced premature auricular and ventricular systoles experimentally in animals, and believe that the ventricular extrasystoles occur with advanced intoxication. Here the auricular extrasystoles disappeared, and ventricular extra beats appeared as an immediate effect after the injection of emetine. It is of interest that R_4 disappeared during the first five days of treatment.

CASE 3.—Another study was made on an East Indian, 60 years of age, who had received no emetine previously. Here we noted an immediate effect from one grain of emetine. The patient later received ½ grain twice a day for eight days. It was discontinued because of diarrhea which was thought to be due to the drug. The only changes of interest in the record occurred in Lead IV. T_4, which was inverted before the injection of the drug, became positive one-half hour after its administration. This may have been due to the reciprocal action on the T waves described by Boyd and Scherf. The position of the electrode over the precordium was the same for each tracing. R_4, which was less than 1 mm. before injection of the drug, became very high. Table III shows the changes as they occurred.

TABLE III

TIME OF MEDICATION	AMPLITUDE OF T WAVES (MM.)				QRS_4		MISCELLANEOUS
	T_1	T_2	T_3	T_4	R_4	S_4	
0	2	3	1.50	−1.50	Very small	Very small	
5 min. after medication	2.50	3	1.50	−1	7	−3	
½ hr. after medication	2	3	1.50	3.50	23	−2	
6th day	2	3	1	−0.50	8	−2	
10th day	2	2	Isoelectric	3	13	−4	Left axis deviation

TABLE IV

TIME OF MEDICATION	SECONDS	AMPLITUDE OF T WAVES (MM.)			
	A-V INTERVAL	T_1	T_2	T_3	T_4
0	0.16	2.50	3.50	0.75	6.50
5 min. after medication	0.17	2	2.50	0.25	4.50
½ hr. after medication	0.18	1.50	1.75	0.25	4.50
5th day	0.18	1.50	2	0.50	2.50

CASE 4.—This was a Latin-American Negro, 30 years of age. Electrocardiograms were made immediately, as in other cases, after an initial dose of one-half grain of emetine subcutaneously. There were slight lowering of the T waves and lengthening of the P-R interval.

CASE 5.—The last case was that of a Latin-American Negro, 27 years of age. He received one-half grain of emetine on the first day, after which the electrocardiograms shown in Table V were taken. One-half

TABLE V

TIME OF MEDICATION	SECONDS	AMPLITUDE OF T WAVES (MM.)			
	A-V INTERVAL	T_1	T_2	T_3	T_4
0	0.16	1.50	3	2	1.50
5 min. after medication	0.16	1.50	3	2	1
½ hr. after medication	0.16	1	2.50	2	1.25
5 min. after second medication	0.16	0.75	2.50	1.50	+0.75 −0.25
½ hr. after second medication	0.16	1	3	1.50	1.50

hour after the first injection, another one-half grain was given, and electrocardiograms were taken again in five minutes and one-half hour. Minor T-wave changes occurred.

DISCUSSION

We have had no unfortunate experiences with emetine hydrochloride as used. Occasionally, when the electrocardiogram shows marked changes, it is best to discontinue medication before the full course is given. Carbarsone has also been used with emetine in some cases, but these patients did not show additional electrocardiographic changes. For the most part, the changes noted are of minor and temporary nature. Most of the patients have had little or no diarrhea during the treatment, but all received supplementary vitamins. The observations in Case 1 make it necessary to consider more severe myocardial effects of the drug. It is possible that mild myocardial infarction occurred in this case. No emetine deaths have occurred at Gorgas Hospital.

CONCLUSIONS

1. Emetine produces minor changes in the electrocardiogram, consisting, for the most part, of T-wave depressions in all leads. These changes are most frequently noted in the limb leads, and are temporary in nature.

2. Emetine hydrochloride, as used in the present study, does not seem to be dangerous, although electrocardiographic studies should be made before and during treatment.

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INCREASED CAPILLARY FRAGILITY IN HYPERTENSION: INCIDENCE, COMPLICATIONS, AND TREATMENT

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In 1940, Paterson[1] stated: "capillary rupture with intimal hemorrhage in relation to the precipitation of coronary thrombi has been described. . . ." by Paterson,[2] Wartman,[3] and Winternitz and his coworkers.[4] He goes on to state: "capillary rupture with intimal hemorrhage is intimately concerned with the mechanism of cerebral arterial thrombosis and possibly, in certain cases, with the causation of cerebral arteriospasm and rupture. It is suggested that the factors responsible for the rupture of intimal capillaries in the cerebral arteries are high intracapillary pressure from hypertension, progressive atheromatous degeneration of the supporting tissue and increased capillary fragility from a variety of causes."

It seemed possible, therefore, that an abnormal condition of the capillaries might be a factor in the production of certain of the vascular accidents which sometimes occur in cases of hypertension. We were especially interested in the relation of such complications to thiocyanate therapy, for we had noted cutaneous ecchymoses rather commonly, retinal hemorrhages less commonly, and apoplexy and coronary occlusion very rarely after the initiation of such therapy. The more serious complications were rare enough to suggest that they were merely coincidental, yet were regarded as alarming nevertheless.

METHOD AND MATERIAL

For a period of eighteen months all persons with hypertension who were routinely studied in our laboratory had, in addition, a measurement of capillary fragility by the Petechial Index of Göthlin,[5] with certain minor modifications.

Technique of the Test.—(1) Mark off a circular area, 6 cm. in diameter, in each antecubital area. Mark off all blemishes and marks in this area that might later be confused with petechiae. (2) Place a standard blood pressure cuff about each arm, and maintain in each a pressure of 35 mm. of mercury for fifteen minutes. Lower the pressure, and count and mark all petechiae within the two circular areas, using a good light and a magnifying lens of 5 D or its equivalent. (3) One hour or more later, repeat, using a cuff pressure of 50 mm. of mercury.

The Petechial Index is calculated as follows: To the number of petechiae occurring at 35 mm. of mercury multiplied by 2, add the additional number occurring at 50 millimeters. Based upon the

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Received for publication Jan. 22, 1944.
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Petechial Index, capillary fragility is considered to be: (a) normal, if the Index is 8 or less, (b) increased (abnormal) if the Index is 13 or more, and (c) borderline, but probably abnormal, if the Index is 9 to 12.

In order to save time, the second stage can be omitted under the following conditions: (1) The number of petechiae after the first stage is 2 or less. Such persons may be considered normal. Usually, but not invariably, the person is normal who has 3 petechiae after the first stage. (2) If 6 or more petechiae appear after the first stage, the subject may be considered abnormal. (3) The test is a repetition, and may be compared with the corresponding first stage of an earlier test. Repetition in less than three weeks, however, is unreliable in any case.

The second stage should always be done if the fragility is being tested in a subject for the first time and there are 4 or 5 petechiae after the first stage. It should also be done in most cases when the number after the first stage is 3.

The patients, 265 in all, had history and physical examination by various members of our hospital staff and referring physicians. Special attention was paid to the following: (1) history suggesting apoplexy, (2) history of spontaneous cutaneous ecchymoses, (3) presence of retinal hemorrhages, as ascertained by ophthalmoscopic examination, and (4) simultaneous medication with thiocyanate.

Ophthalmoscopic examination was carried out by physicians with varying degrees of skill, so that the occurrence of retinal hemorrhages as a positive sign may be accepted, whereas their absence did not necessarily entirely exclude them.

The period of study was never less than six months nor more than twenty months.

Thirty-three patients with increased fragility were treated with Hesperidin* by mouth in a dose of 250 to 500 mg. three times a day, and nine more were given Hesperidin Methyl Chalcone* by mouth in a dose of 10 mg. three times a day. In addition, fourteen such patients were treated with Rutin, the result of which has already been reported.[6]

RESULTS

1. Incidence of increased capillary fragility: As shown in Fig. 1, capillary fragility was found to be normal in 218 of the series, or 82 per cent (approximately). It was definitely increased in 44 subjects, whereas, in three, it was borderline, making a total of 47 persons, or 18 per cent (approximately), whose capillary fragility was, at least, not normal. Judging from the occurrence of complications, it appears that the borderline group should be classed as definitely abnormal.

2. Relation of capillary fragility to sex and age: As shown in Fig. 1, there was no significant relationship between capillary fragility and either sex or age.

3. Relation of capillary fragility to blood pressure level: Fig. 2 shows the systolic and diastolic blood pressure of 54 patients with increased capillary fragility. There was obviously no relationship between the occurrence of increased capillary fragility and blood pressure level. This series of 54 patients was obtained by adding to the

*Supplied by Abbott Laboratories, North Chicago, Ill.

original series of 47, seven subjects from an earlier group who were called back for study because they had developed one or more of the "complications" of increased fragility.

4. Relation of capillary fragility to the occurrence of apoplexy: A history of apoplexy, followed by paralysis, was obtained in four cases, or 2 per cent (approximately) of the patients whose capillary fragility was normal. Four more subjects in this group gave an atypical history, namely, that a diagnosis of apoplexy had at one time been made (usually a severe headache was described as a "slight stroke"), but there never was any paralysis, nor were there any neurological sequelae at the time the patient was studied. If these were included, it would raise the incidence of apoplexy in the group with normal fragility to 4 per cent. On the other hand, seven of the patients with increased fragility gave a definite history of apoplexy followed by paralysis, and five more had strokes during the period of observation, making a total incidence in the group of twelve, or 25 per cent (approximately). It would appear, therefore, that apoplexy occurred with greater frequency in persons with hypertension associated with increased fragility than in those with normal capillary fragility.

5. Relation of capillary fragility to the occurrence of retinal hemorrhages: Retinal hemorrhages were recognized in five persons with normal capillary fragility, or 2 per cent (approximately), and in ten persons, or 21 per cent (approximately), whose capillary fragility was increased. It seems likely, therefore, that retinal hemorrhages occur more commonly in those persons with hypertension whose capillary fragility is increased.

6. Relation of capillary fragility to thiocyanate medication: Ten persons were studied who were attending our dispensary and receiving thiocyanate prior to the beginning of this investigation. These persons were chosen because all of them showed either cutaneous ecchymoses (nine cases) or retinal hemorrhages (one case) beginning soon after the onset of thiocyanate medication. All ten persons showed an increase in capillary fragility. Three other patients with increased capillary fragility were given thiocyanate without other treatment. One patient developed cutaneous ecchymoses, one developed retinal hemorrhages, and the third died of a stroke. We have not felt justified in continuing this phase of the study, but have made it a rule never to give thiocyanate to a patient with increased capillary fragility until, or unless, that fragility has become normal as the result of treatment. Thiocyanate therapy has been used in twelve such cases without incident.

7. Relation of capillary fragility to mortality: During the twenty months' period of study there were three deaths in the group with normal fragility, or 1 per cent (approximately), and five deaths, or 10 per cent (approximately), in the group with increased fragility. It seems probable that the mortality is greater among persons with

hypertension and increased capillary fragility than among those with hypertension and normal fragility.

8. Effect of treatment: Hesperidin was given to 33 persons with increased capillary fragility, only 23 of whom were adequately fol-

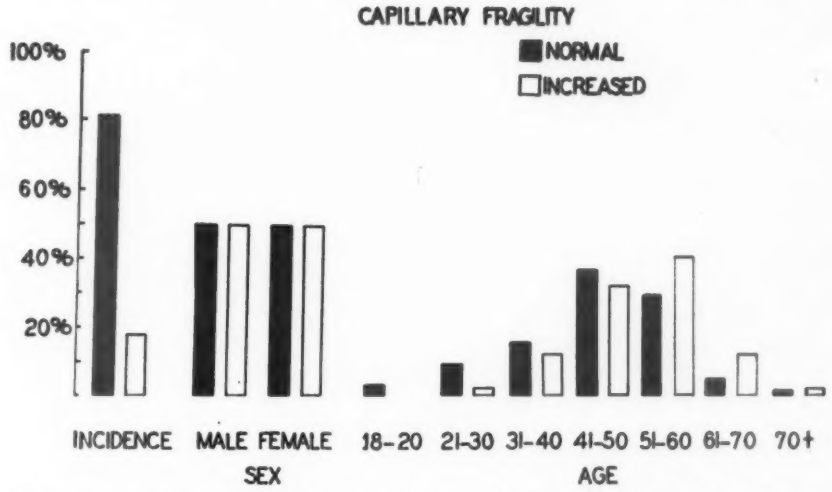

Fig. 1.—Chart comparing the incidence of normal and increased capillary fragility in the general hypertensive group (on the left) and in groups selected on the basis of sex and age. The figures for the two columns on the left are expressed as percentage of the entire group of 265 cases. The percentage figures for sex and age, however, refer only to the total groups with normal fragility (filled-in rectangle) or increased fragility (open rectangle). The age is expressed in years.

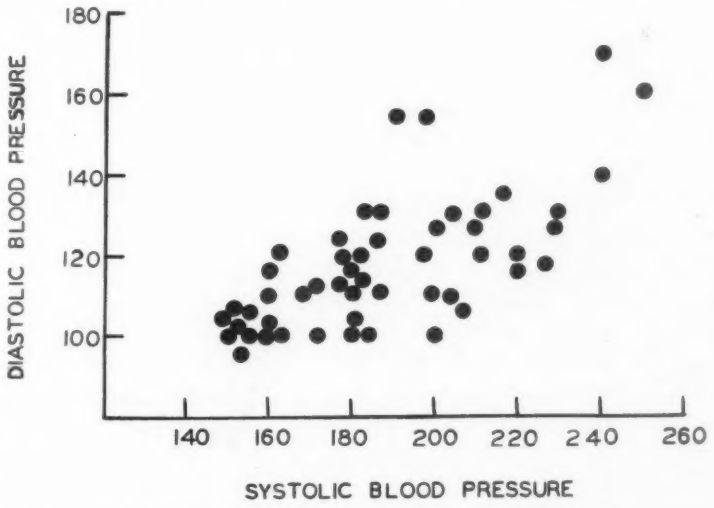

Fig. 2.—Chart showing the systolic and diastolic blood pressure of 54 persons with increased capillary fragility. Each dot represents one subject.

lowed. In 20 of these, capillary fragility, as measured by Göthlin's test, became normal within one or two months after starting treatment, and remained so thereafter except in two instances, in which the pa-

tient discontinued treatment without permission, when the test became abnormal, to become normal again when treatment was resumed. In three subjects the capillary fragility was not affected by treatment and remained abnormal; two of these developed apoplexy and died. One of the 20 patients whose fragility returned to normal after therapy also died of apoplexy. This patient had a high degree of papilledema when first seen.

Hesperidin methyl chalcone was given to nine persons with increased capillary fragility. In seven of these the fragility became normal, while two were unaffected. This group has been followed only six to nine months, and no complications have occurred in any of the nine subjects.

We have not felt justified in discontinuing medication at intervals to secure adequate controls for its effectiveness. Also, one cannot say with the evidence at hand that reversion of Göthlin's test to normal indicates that the subject is less likely to suffer one of the hemorrhagic complications of hypertension, but it seems likely that such is the case.

SUMMARY

1. Capillary fragility was increased in about 18 per cent of 265 cases of hypertension. This incidence was not related to sex, age, or degree of hypertension.

2. Persons with increased capillary fragility are especially predisposed to apoplexy, retinal hemorrhage, and death.

3. Thiocyanate tends to make worse a previously abnormal fragility, or perhaps in certain cases may even change fragility from normal to increased. When this occurs, thiocyanate may be a factor in the causation of apoplexy and other hemorrhagic phenomena.

4. Hesperidin and hesperidin methyl chalcone restored fragility to normal in about 84 per cent of cases of increased capillary fragility. It is hoped, but not yet proved, that this may also lessen the frequency of the complications of increased capillary fragility.

5. It is probable that thiocyanate should not be given to persons with increased capillary fragility, unless or until that fragility has become normal as the result of therapy. After this has been done, thiocyanate apparently can be given with impunity.

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BLOOD PRESSURE IN THE ARM AND THIGH OF MAN

I. A Study of Averages, Variations, and Differences Between Thigh and Arm

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THE blood pressure in the extremities of man has been of interest ever since blood pressure could be measured clinically, yet many questions relative to it remain unanswered. For example, there have been assertions and denials that the blood pressure in the legs of the recumbent subject is higher than that in the arms. Those who believe it is do not agree on the explanation of this physiologic curiosity. Many physicians forget that variations of blood pressure occur in so-called normal persons, and the attempt to ascertain "normal" responses as a result of study of small groups of subjects has been invalidated in some degree by the variability. The value of studies limited to the influence of a single factor, such as posture, for example, is limited because factors other than posture are not considered at the same time. It is easy to err in conclusions relative to the physiology of the circulation by noting the changes of pulse rate in one group of subjects, the reactions of blood pressure in another group of subjects, studied perhaps under entirely different experimental conditions, and the effects of exercise on a third group of subjects under still different circumstances. The present studies were on the influence of several factors on blood pressure in the same group of patients.*

HISTORICAL ASPECTS

Since 1908, numerous investigators[1-18] have studied blood pressure in the four extremities. Prior to 1924, it was generally felt that the blood pressure in the legs was not higher than that in the arms of normal subjects, provided the hydrostatic effect (head higher than the feet) was excluded. In 1924, Bazett,[1] by direct methods, noted in dogs a higher systolic pressure in the brachial than in the carotid artery. The systolic pressure in the femoral was higher than that in the brachial artery, but the diastolic pressure was the same throughout the arterial tree. He hypothesized a possible mechanism for such differences of pressure, which involves the transformation of the greater kinetic energy in the legs into stress or pressure energy. Burdick and his associates,[2] who studied four normal subjects by a photographic technique, concluded that the blood pressure in the thighs of resting subjects in the horizontal posture was 38 mm. higher than in the arms. This figure increased to 67 mm. with exercise. In 1929,

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Received for publication Jan. 25, 1944.
*This is the first of a series of papers reporting the results of these studies.

Strang,[16] after a careful study of fifty-four normal people, concluded that the blood pressure in the legs is higher than that in the arms, regardless of the position of the body; the average difference was 33 mm. of mercury. Hamilton and his associates'[17] studies of blood pressure, in 1936, by direct arterial punctures on thirty human subjects left no doubt that the blood pressure is higher in the legs than in the arms, even when subjects are in the horizontal posture. Cady[3] consistently found a higher systolic pressure in the popliteal than in the brachial artery. The difference was greatest in hypertensive subjects and in those who received drugs causing arteriolar constriction. After lumbar sympathectomy and after the use of drugs which caused arteriolar relaxation, it was smaller. In dogs the blood pressure measured by arterial puncture was higher in the femoral than in the carotid artery.

PROCEDURES

The 112 unselected subjects of this study* had a wide variety of clinical states, many of which were not organic. With the exception of two cases of essential hypertension, the subjects did not have any significant vascular disease. Sixty-nine of the subjects were male and forty-three were female. Their ages ranged from 12 to 65 years; the average was 39.7 years. During the course of all the studies, including those which are to be reported in subsequent papers, 2,415 measurements of blood pressure and 635 counts of the pulse rate were recorded. Subjects sat on the examining table for one to two hours, during which time a neurological history and examination were carried out. At the close of the examination, the subject lay on the table with the arms and legs in the horizontal position. A Tycos aneroid sphygmomanometer† cuff which was 5½ inches (14 cm.) wide was then placed around the left arm, and a leather-covered pneumatic cuff, 5 inches (12.7 cm.) in width, held in place by straps and buckles, was placed around each thigh just above the knee. The point at which the first Korotkoff sound was heard was accepted as the systolic blood pressure, and that point at which the sounds were suddenly muffled was taken as the diastolic pressure. In most instances, this latter point was definite. After subjects had been in the horizontal posture for about five minutes, blood pressure readings in the left arm, right thigh, and left thigh were taken in that order, after counting the pulse rate. After two minutes, a second series of blood pressures and pulse rates was recorded. In most instances, the left thigh cuff was rapidly inflated to a point greater than the estimated systolic blood pressure in the standing posture. The subject then assumed the standing posture and remained quiet. At the end of one minute in that position the pulse rate was counted, after which the blood pressure was measured in the right thigh. The cuff around the left thigh was then deflated, during which process the blood pressure was measured. Two minutes later, in a second series of studies, the blood pressure was measured in the left arm, right thigh, and left thigh, in that order,

*The authors wish to express their appreciation to Dr. Woltman, of the Section on Neurology, for his courtesy in permitting the use of patients for study, and to Dr. Allen, of the Division of Medicine of the Mayo Clinic, for helpful suggestions and criticisms in connection with these studies.

†Accuracy was determined by checking against a mercury sphygmomanometer.

and the pulse rate was counted. The subject then assumed the supine position. An identical series of studies was made at the end of one minute and again at the end of three minutes in this posture.

CRITICISMS

Obviously, the methods which were employed in this study are subject to some criticism. We are fully aware of the lack of precision and control, which might in part be obviated were one working with trained animals under laboratory conditions. However, it is felt that the conditions of study were sufficiently accurate to denote trends, and, above all, to demonstrate the marked variability of vascular response which may occur in the same person and among different persons. If this study does nothing more than emphasize the importance of biologic variability, it will have been worth while.

That estimation of the diastolic pressure is subject to more error than is that of the systolic is widely appreciated. This is especially true when congestion of the leg caused by standing or by slow deflation of the pressure cuff renders the diastolic sound feeble and poorly demarcated.

The old question arises as to the accuracy of indirect measurement of blood pressure. Although this method is not as accurate as the direct one, Hamilton and his associates[7] have stated, as a result of intra-arterial measurements of blood pressure in man, that the indirect method is accurate enough for most purposes.

Simultaneous measurement of blood pressure in the arm and leg was not possible. That this might lead to errors in interpretation is well appreciated. However, the magnitude and direction of the observed changes were so great and consistent as to leave little doubt of their significance. Strang[16] studied the blood pressure in the arm just before and just after measuring the blood pressure in the thigh, but did not note any significant differences between readings made under those circumstances.

In some respects, it might have been desirable to tilt subjects passively to the upright posture, but this was not feasible. Strang found that the effect of tonic contraction of muscles incident to standing was rather small, but was greater in the leg than in the arm.

The question arises as to whether a 5-inch cuff (12.7 cm.) is wide enough for measuring accurately the blood pressure in the thigh of an obese person. Erlanger and Hooker[19] stated that if the artery is compressed as much as 4 cm. the cuff is adequate. Wiggers[20] has stated that a cuff which is 13 cm. in width is ample. The cuffs which we used largely satisfied this criterion, and were constructed in such a way as to prevent any ballooning about the margins of the cuff. They were, of course, a source of some discomfort. Wider cuffs would have added to the discomfort, probably without increasing the accuracy of the readings.

RESULTS

The average values for the blood pressure, for pulse pressure, for difference of blood pressure between the arm and the thigh, and for pulse rate in both postures in 112 cases are to be found in Fig. 1 (derived from Table I). The systolic pressure in the arm remained unchanged, but the systolic and diastolic pressure in the thigh, the systolic and diastolic differential in pressure between thigh and arm, and the pulse rate increased on standing. The pulse pressure decreased in the arm and thigh, but to a greater extent in the arm, mainly because the systolic pressure failed to increase along with the diastolic pressure on standing. For the same reason, there was a greater increase in systolic than in diastolic thigh-arm differential* pressure.

TABLE I

MAXIMAL, MINIMAL, AND AVERAGE VALUES FOR THE SYSTOLIC AND DIASTOLIC BLOOD PRESSURE AND PULSE PRESSURE IN THE ARM AND THIGH, DIFFERENTIAL PRESSURE (MILLIMETERS OF MERCURY), AND PULSE RATE. HORIZONTAL AND STANDING POSTURE. 112 CASES

	PRESSURE	HORIZONTAL			STANDING		
		MAX.	MIN.	AV.	MAX.	MIN.	AV.
Arm	Systolic	234	94	115	244	80	115
	Diastolic	144	56	77	144	54	83
	Pulse pressure	90	16	38	100	8	32
Thigh	Systolic	296	100	150	310	100	193
	Diastolic	188	42	104	258	76	149
	Pulse pressure	104	14	46	76	10	44
Differential blood pressure	Systolic	64	−4	35	128	−4	78
	Diastolic	60	−20	27	104	2	66
Pulse rate		100	48	75	124	56	94

TABLE II

DIRECTION AND AVERAGE DEGREE OF CHANGE (IN MILLIMETERS OF MERCURY) OF ARM AND THIGH PRESSURES IN SUCCESSIVE READINGS AT ONE AND THREE MINUTES IN EACH POSTURE. 112 CASES

PRESSURE	POSTURE	ARM		THIGH	
		1 MIN.	3 MIN.	1 MIN.	3 MIN.
Systolic	Lying		−3		+ 3
	Standing	+1	−1	+43	+43
Diastolic	Lying		−1		+14
	Standing	+6	+6	+37	+45

The failure of the systolic pressure in the arm to rise while the diastolic pressure in the arm increased an average of 6 mm. on standing is in general keeping with the observations of many observers,[21-27] who have found that the diastolic pressure in the arm rises an average of 10 to 12 mm. while the systolic pressure in the arm may rise, remain stationary, or decrease with assumption of the standing posture. The systolic pressure in the thigh did not change materially on successive readings (Table II). This was also true for the diastolic pressure in

*Hereafter, for the sake of brevity, the term "differential" will denote the difference between the blood pressure in the thigh and that in the arm. Normally, blood pressure in the thigh is higher than in the arm.

the arm, but, in the thigh, the second diastolic reading, while the subject was horizontal, was, on the average, 14 mm. higher than the first. In the standing posture, the second diastolic reading averaged 8 mm. higher than the first.

The extent of variation of blood pressure from the average for the group is indicated in Table III. Thus, only 59.5 per cent of all the blood pressures fell within 10 per cent of the average, whereas 86.5 per cent of the readings fell within 20 per cent of the group average.

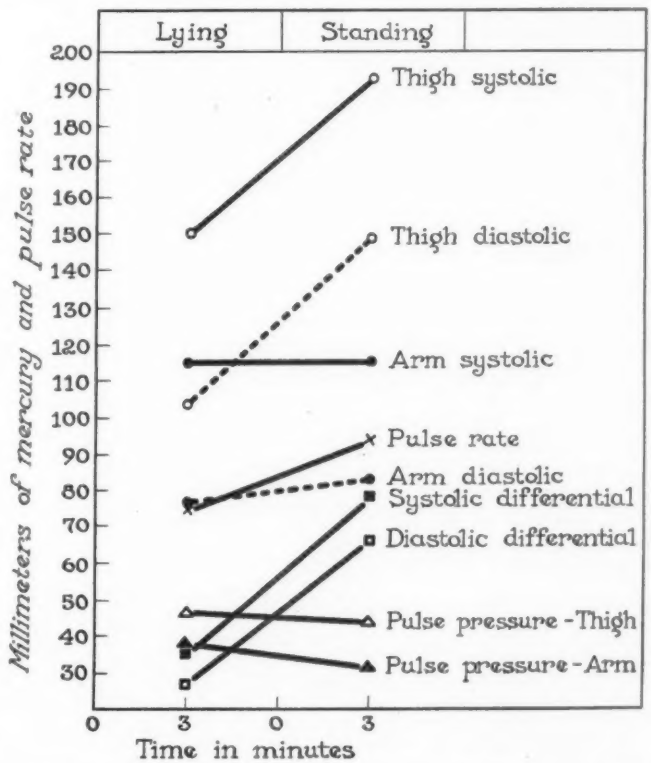

Fig. 1.—Average values for systolic and diastolic blood pressure and pulse pressure in the arm and thigh, differential blood pressure, and pulse rate of 112 subjects in horizontal and upright postures.

These results are almost identical with those of Strang, who found in a careful study of fifty-four normal subjects that 60 per cent of the blood pressure readings fell within 10 per cent, and 85 per cent of the readings fell within 20 per cent, of the average for the group. In general, in the present study, the greatest tendency to vary from the average was found in the systolic pressure in the thigh, followed, in order, by the diastolic pressure in the thigh in the horizontal position. The least variability was noted in the systolic pressure in the arm in the horizontal position and in the diastolic pressure in the arm in the standing posture.

That there is considerable variation in the difference between blood pressures in the thigh and arm can be seen from Table I. Thus, in the horizontal posture, the systolic differential pressure varied from −4 to +64 mm., with an average difference of 35 mm., and the diastolic differential varied from −20 to +60 mm., with an average difference of 27 mm. of mercury. In the upright posture, the systolic differential varied from −4 to +128 mm., and the diastolic varied from +2 to +104 mm.; the average for the former was 78, and, for the latter, 66 mm. of mercury. A negative differential pressure was observed in only two cases.

Table IV lists various values for the difference in blood pressure between the thigh and arm as observed by various authors. The average for all groups, including ours, is 31.6 mm. of mercury; that is, the blood pressure in the thigh averages that much higher than in the arm.

TABLE III

VARIATIONS OF OBSERVATIONS FROM THE AVERAGE FOR EACH POSITION

	PLACE	POSITION	AVERAGE PRESSURE		OBSERVATIONS ± 10 PER CENT OF AVERAGE		OBSERVATIONS ± 20 PER CENT OF AVERAGE	
			CASES	MM.	CASES	PER CENT	CASES	PER CENT
Systolic pressure	Arm	Lying	105	115	64	61.4	96	91.4
		Standing	96	115	55	57.3	87	90.6
	Thigh	Lying	107	150	56	52.3	86	80.4
		Standing	100	193	58	58.0	92	92.0
Diastolic pressure	Arm	Lying	105	77	62	59.4	86	81.9
		Standing	96	83	59	61.4	99	94.3
	Thigh	Lying	107	104	59	55.1	80	76.2
		Standing	100	149	71	71.0	85	85.0
Average			102	123	60.5	59.5	88.8	86.5

TABLE IV

COMPARATIVE STUDIES ON SYSTOLIC BLOOD PRESSURE DIFFERENTIAL BETWEEN THIGH AND ARM IN HORIZONTAL POSTURE

AUTHOR	YEAR	CASES	TYPES OF CASES	DIFFERENCE		METHOD
				AVERAGE	RANGE	
Burdick and others	1925	4	Normal	38	?	Photographic
Strang	1929	54	Normal	38	?	Auscultatory
Glasermann	1932	10	Normal	30	?	Auscultatory
		7	Anemia	53	?	Auscultatory
		26	Aortic regurgitation	46	?	Auscultatory
Cady	1939	75	Essential hypertension	38	6 to 88	Auscultatory
		75	Nonhypertensive	22	11 to 30	Auscultatory
Gambill and Hines	1941*	112	Miscellaneous† (including 2 hypertensive)	35	−4 to +64	Auscultatory

*Present paper is a report of the results of this study, which was conducted in 1941.

†One hundred ten of these had essentially normal blood pressure.

TABLE V

CASES ACCORDING TO HIGHEST HORIZONTAL THIGH PRESSURE BASED ON SIXTY-NINE CASES

PRESSURE	LEFT THIGH BLOOD PRESSURE HIGHEST		RIGHT THIGH BLOOD PRESSURE HIGHEST		EQUAL BLOOD PRESSURE IN THIGHS
	CASES	AVERAGE, MM.	CASES	AVERAGE, MM.	CASES
Systolic	28	5	31	8	10
Diastolic	27	7	29	9	13

If one considers only normal persons, fairly close agreement will be found among various authors.

Although the blood pressure, on the average, appeared to be slightly higher in the right than in the left thigh, this difference does not appear to be significant except in certain cases in which there are unilateral lesions of the central nervous system. Comparative values between blood pressure in the right and left thighs in 69 of the 112 cases are listed in Table V.

In considering various factors which might affect the thigh-arm differential blood pressure, it seemed desirable to compare the effects of so-called spastic and flaccid types of involvement of an extremity.

Pitfield,[28] in a study of normal subjects and subjects suffering from organic cerebral lesions, chiefly hemiplegia, noted that the blood pressure in the limb contralateral to the cerebral lesion responded with much greater changes to tapping over the brachial artery than did the blood pressure in the homolateral limb. This change was chiefly in the diastolic pressure, which either rose or fell. These differences were not observed among his control cases. It was suggested that certain brain lesions may thus render the blood pressure in the affected limb more labile and less subject to the influence of higher vasomotor control.

With the foregoing in mind, a tabulation was made of cases in which there were unilateral cerebral or spinal lesions. There were eight such cases in this series. A rough grouping into those in which there were spastic, and those in which there were flaccid, types of involvement of an extremity was made. The results are listed in Table VI.

It was expected that possibly those in which there was spastic involvement might have a higher, and those in which there was flaccid involvement a lower, blood pressure in the affected than in the normal limb. This seemed to be true for Cases 47, 68, 72, and 94. In the other four cases this difference was less striking. Cases 47 and 68 are especially worthy of comment, for these patients had a considerably higher blood pressure in the spastic thigh than in the normal thigh. In these two cases, the differences were probably significant, for differences of pressure between the two thighs for the entire series of 112 cases were not nearly so great as among the foregoing cases. In

TABLE VI

COMPARISON OF DIFFERENCES OF BLOOD PRESSURE (IN MILLIMETERS OF MERCURY) IN THE TWO THIGHS IN THE STANDING POSTURE. INDIVIDUAL DIFFERENCES IN EIGHT CASES IN WHICH THERE WERE UNILATERAL NEUROLOGIC LESIONS, AND AVERAGE DIFFERENCES FOR RIGHT AND LEFT THIGHS IN SIXTY-NINE CASES*

CASE	DIAGNOSIS	AFFECTED SIDE DIFFERS BY:		TYPE DISTURBANCE	
		SYSTOLIC	DIASTOLIC	SPASTIC	FLACCID
47	Right spastic hemiplegia, 15 months' duration	+ 2	+28	+	
68	Left parkinsonism	+54	+38	+	
101	Right spastic hemiplegia, 7 years' duration. Very little residual	− 1	− 6	+	
107	Bilateral parkinsonism (left > right)	−18	+24	+	
88	Right spastic hemiplegia (ancient)	− 4	0	+	
72	Protruded disk (atrophy, decreased reflexes)	−46	−38		+
86	Protruded disk (atrophy, weakness of limb)	−12	+14		+
94	Atrophic left leg (since a child). Left patellar and Achilles reflexes much decreased; left abdominal reflex absent	−20	−16		+

*Average difference between right and left thigh in sixty-nine miscellaneous cases, including the above, was systolic, 6; diastolic, 8.

Cases 88 and 101 the extremity had been paralytic for years, and the blood pressures in the affected limb were not much different from those on the normal side. Could it be that blood vessels in the affected limb had readjusted their tonicity gradually over a period of years to harmonize with the general level of blood pressure?

COMMENT

Although the factors of excitement and discomfort from the use of the tight cuff may have contributed in some degree to the wide variations which were noted in blood pressure and pulse rate among some subjects, other factors would seem to be of greater importance. Outstanding among them would seem to be the differences of constitutional make-up among different persons which help determine the response of blood pressure in the resting, unstimulated states, as well as the response to an emotional or painful stimulus. Realization of this fact suggests greater caution in attributing declines or increases of blood pressure to the effects of a given therapeutic procedure. The factor of variability is even more important among those who have essential hypertension and among vascular hyperreactors without hypertension.

It is not within the scope of this paper to discuss the various hypotheses which have been advanced to explain the difference of blood pressure in the thigh and arm. We agree with Strang[16] that two components are apparently responsible for such differences: a hydrostatic and a dynamic component. It is the latter which permits vascu-

lar readjustment over a wide range, and which is necessary to meet the varying needs of the living organism.

The reason why, in two subjects, the blood pressure was lower in the thigh than in the arm is not understood. The blood pressures in these cases were checked several times with the thought that some error had been made, but none could be found.

SUMMARY

Blood pressure, pulse pressure, the difference of blood pressure in thigh and arm, and the pulse rate in 112 subjects in the horizontal posture showed great variability from person to person.

The tendency of the diastolic blood pressure to increase while the systolic blood pressure remained essentially the same on changing from the horizontal to the standing position is in agreement with the results reported by others.

Fifty-nine and five-tenths per cent of all blood pressures fell within 10 per cent, and 86.5 per cent fell within 20 per cent, of the average for the group. These results are almost identical with those of Strang.[16]

Differential blood pressures between thigh and arm revealed a wide range of values; the average was 35 mm., systolic, and 27 mm., diastolic, for the horizontal posture. Assumption of the standing posture resulted in a differential pressure of 78 mm., systolic, and 66 mm., diastolic.

No apparent correlation was noted between differential pressures and factors such as age, sex, or occupation.

No significant differences were found between blood pressures in the left and right thighs of normal subjects.

Knowledge of the range of blood pressure in the normal, nonhyperreacting subject, as contrasted to that in the normal, hyperreacting, or hypertensive, hyperreacting subject, is particularly important for those who are trying to evaluate therapeutic attempts to lower or raise the blood pressure.

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BLOOD PRESSURE IN THE ARM AND THIGH OF MAN

II. Hydrostatic Influences

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THE purpose of this study was to attempt to evaluate the hydrostatic factor in the changes of blood pressure which are associated with assumption of the upright posture. This is the second of a series of papers reporting the results of a number of different studies on a group of subjects. For a general discussion of purposes, criticisms, and techniques, the reader is referred to the first of this series of papers.[1]

Hill, Flack, and Holtzman[2] found a definite correlation between the theoretical and observed increases of blood pressure that occur on assumption of the erect posture. The theoretical increase due to hydrostatic pressure was nearly the same as the actual increase. Strang[3] made similar calculations, and expressed the opinion that the increase of blood pressure with change to the upright posture is due almost entirely to hydrostatic pressure, although he felt that a vasopressor homeostatic component may also contribute to the increase.

In the present investigation the influence of hydrostatic pressure was studied by three approaches. First, in 50 of the 112 subjects, the cuff on one thigh was inflated, before the subject stood, to a point well above the systolic blood pressure in the thigh in the upright posture. After the subject had stood for one minute the blood pressure in the opposite thigh was taken, after which the blood pressure was recorded on the side with the inflated cuff; the reading was made as this cuff was deflated. Readings were repeated in the same order in each thigh one minute later for comparison. Although prior inflation of the cuff on one side does not obviate hydrostatic pressure, it does apparently modify, momentarily, the blood pressure immediately after the hydrostatic column is abruptly lengthened by deflation of the cuff.

Second, the approximate value of hydrostatic pressure at the level of the popliteal space was calculated in the upright posture by measuring the distance in centimeters from the left fourth intercostal space near the sternum to the lower border of the thigh cuff in the popliteal space. By means of the following formula, used by Strang, the value of hydrostatic pressure in millimeters of mercury was obtained: $\frac{\text{Distance in millimeters}}{13.6} \times 1.05 =$ millimeters of mercury. In this instance, 1.05 represents the specific gravity of blood and 13.6 represents the ratio of the specific gravity of mercury to that of water. Thus, the calculated hydrostatic pressure was compared with the observed increase of pressure which occurred on standing. These calculations were done on 26 of the 112 subjects.

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Received for publication Jan. 25, 1944.

Third, the effect of elevation of the arm or thigh on the blood pressure was observed. In twenty-six cases the arm was elevated to an angle of 90 degrees with reference to the horizontal position, and the resulting blood pressure was noted at the end of one minute. In fourteen cases the thigh was elevated semipassively to angles of 35 and 90 degrees with the horizontal, and then the blood pressure was noted at the end of one minute. The latter procedure is open to criticism because one could not always obtain relaxation of the hamstring tendons. Variations of the contraction of these tendons could possibly affect the accuracy of the readings.

RESULTS

Use of the thigh cuff on one thigh in the first study showed a net decrease of 8 mm. (33 per cent) in the systolic, and a decrease of 17.6 mm. (10.8 per cent) in the diastolic, blood pressure; the opposite thigh was used as a control. The decrease of pressure was observed for only a few seconds during, and immediately after, deflation of the previously inflated cuff. Within thirty to sixty seconds after deflation of the cuff, the blood pressure on the experimental side was usually back to the level of the control thigh. The results are shown in Table I.

The foregoing observations are probably significant because it was found[1] that blood pressures while patients were in the horizontal posture were essentially the same in both thighs in most cases. The exact reason for the foregoing differences is not clear. One might reason that, while the cuff is kept inflated above systolic pressure in the upright posture, the vessels below the cuff are spared the internal stretching force which otherwise would be exerted by the hydrostatic pressure of the column of blood below the heart. They thus tend to relax. However, whenever the pressure in the cuff is lowered below the diastolic level, the full hydrostatic load of the column of blood above the cuff is thrown on the relaxed vessels below the cuff. They perhaps soon regain their constrictor tone under the influence of the resulting internal stretching force of hydrostatic pressure. In this connection one may recall that Bayliss,[4] many years ago, demonstrated that arteries contract and relax in response to variations of internal pressure.

The possibility that local vasodilating substances, such as histamine, might be elaborated in the leg rendered ischemic by the tight cuff and act locally on the vessels of that leg is to be considered.

TABLE I

DIFFERENCES IN ORTHOSTATIC BLOOD PRESSURE IN MILLIMETERS OF MERCURY BETWEEN RIGHT AND LEFT THIGH, INDUCED BY INFLATION OF ONE THIGH CUFF ABOVE SYSTOLIC PRESSURE PRIOR TO ASSUMPTION OF ERECT POSTURE

CASES	PRESSURE	CONTROL DIFFERENCES	DIFFERENCES DUE TO CUFF	NET DIFFERENCES	DECREASE OF BLOOD PRESSURE DUE TO CUFF (%)
50	Systolic	−2.0	−10	− 8.0	3.0
50	Diastolic	−0.4	−18	−17.6	10.8

The results of the second study, carried out on twenty-six subjects, are to be found in Table II. Thus, the increase of blood pressure in the thigh on change of subjects from the horizontal to the upright posture, calculated on the basis of hydrostatic pressure, was 6.6 per cent higher for the systolic, and 2.5 per cent higher for the diastolic, pressure than the increases which were actually observed. Theoretically, one would rather have expected the observed pressure to be greater than the calculated pressure, if they differed at all. To explain the foregoing observation one might assume that an impairment of the compensatory homeostatic factors concerned in the regulation of the blood pressure occurs when the subject is moved to the upright posture. Strang, in his study of twenty-four subjects, found that the difference between the observed and calculated changes of blood pressure on assumption of the upright posture were less than 2 per cent. It would appear that most of the rise of blood pressure which occurs when subjects stand is the result of hydrostatic pressure. The potential role of homeostatic factors is, however, illustrated in some instances in which pressures in the upright posture exceed considerably the calculated or theoretical pressures.

The results of the third study, namely, the effect of semipassive elevation of arm and thigh, are revealed in Table III. Thus, the systolic pressure in the arm was lowered about 17 per cent, and the diastolic

TABLE II

BLOOD PRESSURE IN THIGH IN DIFFERENT POSTURE: OBSERVED COMPARED WITH THEORETICAL. AVERAGE VALUES IN TWENTY-SIX CASES

	POSITION	BLOOD PRESSURE, THIGH	BLOOD PRESSURE, STANDING MINUS LYING	HEART TO POPLITEAL SPACE (CM.)	EQUIVALENT, MM. OF MERCURY	THEORETICAL PRESSURE	THEORETICAL PRESSURE MINUS ACTUAL	DIFFERENCE (%)
Systolic pressure	Lying	152						
	Standing	197	45	75.6	58	210	+13	+6.6
Diastolic pressure	Lying	106						
	Standing	160	54	75.6	58	164	+ 4	+2.5

TABLE III

EFFECT OF SEMIPASSIVE ELEVATION OF ARM OR THIGH ON BLOOD PRESSURE IN THAT ARM OR THIGH

	CASES	PRESSURE	HORIZONTAL	ELEVATED 1 MIN.	CHANGE	CHANGE (%)	APPROXIMATE ANGLE OF ELEVATION (DEGREES)
Arm	26	Systolic	119	99	–20	–16.8	90
		Diastolic	77	59	–18	–23.3	
Thigh	14	Systolic	160	148	–12	– 7.5	35 to 90 (Av. 66)
		Diastolic	111	96	–15	–13.5	

pressure was lowered about 23 per cent by such procedures. The systolic pressure in the thigh decreased, on the average, 7.5 per cent, and the diastolic pressure decreased 13.5 per cent on elevation of the limb.

That the decrease of blood pressure which occurs in the limb which is elevated may not be due entirely to hydrostatic pressure is suggested by the following observations made on one of us (E. E. G.): The control blood pressure when the thigh was in the horizontal position was 142/96. After elevation of the thigh to approximately 80 degrees for one minute, the pressure was 102/78. The foot was then flexed and extended in that position ten times during a period of ten to fifteen seconds. The pressure in the thigh immediately after this exercise was 100/58. The blood pressure one minute after assumption of the horizontal position was 138/88. Emptying of the venous reservoir or some other change as the result of the exercise must have affected the homeostatic component of blood pressure, for, obviously, hydrostatic pressure was constant before and after exercise.

SUMMARY

Placing a cuff around the thigh and inflating it above the level of systolic blood pressure before subjects assumed the standing posture resulted in a significant, but rather transient, lowering of blood pressure in that thigh when the blood pressure was measured during the period of deflation of the cuff. Possible explanations for this observation are suggested.

It appears that most of the increase which occurs in the blood pressure in the thigh when one stands is due to the influence of hydrostatic pressure. There is, however, in a few subjects a homeostatic component in such increases; this is variable, and is distinct from that due to hydrostatic pressure. This homeostatic component may be of considerable magnitude.

Elevation of the arm or thigh above the horizontal position resulted in a decrease of blood pressure in the limb; this is apparently also largely related to hydrostatic factors.

The posture of a limb in which the blood pressure is measured should be stated, particularly when the limb is not in the horizontal position. For obvious reasons, the horizontal position of the limb is the one in which blood pressure should be measured.

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BLOOD PRESSURE IN THE ARM AND THIGH OF MAN

III. Effect of Venous Engorgement

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WE HAVE been impressed with the observation that venous congestion often seems to result in an increase in the diastolic pressure. In some instances this may amount to several millimeters. The fact that some persons have this tendency, whereas others do not, requires clarification. The purpose of this study was to learn something about the effects of congestion, produced by various means, on blood pressure in the arm and leg while subjects were in the horizontal and erect (head-up) posture, and to study individual differences. Three types of study were performed, utilizing different groups of persons among the 112 people upon whom studies were reported in the first of this series of papers.[1]

STUDY 1

This study consisted of observing the effect of relatively prolonged engorgement of one leg, produced by keeping the pressure within the cuff about the thigh above the level of diastolic pressure, but 10 to 15 mm. below systolic blood pressure, for three minutes. The blood pressures during this time were measured in the noncongested and congested limb, in that order, at the end of the first and third minutes, and then again one minute after deflation of the congesting cuff. This study comprised twenty-four cases in which the limb was in the erect posture and fourteen cases in which the limb was in the horizontal posture.

Results.—Congestion of the leg which was in the erect, foot-down position produced a net decrease of 1 mm. of mercury (0.5 per cent) in the systolic pressure, as compared with that in the noncongested leg, which was used as a control (Table I). This is, of course, an insignificant change. The diastolic pressure, in contrast, increased a net average of 13 mm. (8.2 per cent), apparently as a result of the congestion. Congestion of the leg which was in the horizontal position produced a net increase of 3.4 mm. (2.2 per cent) in systolic pressure and 11 mm. (10.3 per cent) in diastolic pressure in that leg when compared with the changes in the noncongested leg. The values for the diastolic pressure are probably significant. In eight cases, congestion of one arm which was in the erect, hand-down position resulted in a net increase of 7.5 mm. in the diastolic pressure, with essentially no change in the systolic pressure.

Division of Medicine, Mayo Clinic.
Received for publication Jan. 25, 1944.

TABLE I

DIFFERENCES IN BLOOD PRESSURE BETWEEN THE TWO THIGHS IN STANDING POSTURE AFTER CUFF PRESSURE IN ONE THIGH HAD BEEN MAINTAINED FOR THREE MINUTES BETWEEN SYSTOLIC AND DIASTOLIC LEVEL

POSITION	CASES	PRESSURE TYPE	CONTROL BLOOD PRESSURE	CONGESTED THIGH	NONCONGESTED THIGH	DIFFERENCE	NET CHANGE (%)
Standing	24	Systolic	204	− 4	−3.0	− 1.0	− 0.5
	24	Diastolic	158	+13	0.0	+13.0	+ 8.2
Lying	14	Systolic	156	+ 3	−0.4	+ 3.4	+ 2.2
	14	Diastolic	107	+18	+7.0	+11.0	+10.3

A study related to the foregoing, employing one of us (E. E. G.) as the subject, consisted of congesting one leg in the following manner: Two cuffs were placed around one thigh, the first high on the thigh and the second just above the knee. A control blood pressure reading, taken in the thigh while the subject was standing, was 200/160. The subject then lay horizontally, and the upper cuff was inflated to 90 mm. of mercury, after which he assumed the standing position. After one minute of congestion in this position the blood pressure in the congested thigh had increased to 224/192. The upper cuff was then completely deflated, after which a second measurement revealed a systolic blood pressure of 210 and a diastolic of 160. Thus, congestion was associated with an increase of 24 mm. in the systolic pressure and of 32 mm. in the diastolic pressure. Discomfort from the procedure was minimal.

STUDY 2

The second study utilized 41 of the 112 subjects referred to in the first of these papers.[1] Two and sometimes three successive measurements of diastolic pressure were made in the arm and thigh; the second and third were made within ten to fifteen seconds of the preceding one. After the first measurement of diastolic pressure had been made, the cuff about the limb, without further deflation, was reinflated a few millimeters above diastolic pressure; after this it was deflated slowly until the diastolic level was again found. These readings were made with the subject standing and with the arm dependent. By the foregoing maneuvers blood could enter the arm and thigh as a result of cardiac systole, but could not get out of the limb. Engorgement of the arm and leg was thus accomplished.

Results.—The second diastolic measurement averaged 3 mm. higher in the arm and 9 mm. higher in the thigh than the first (Table II).

TABLE II

COMPARISON OF TWO SUCCESSIVE DIASTOLIC PRESSURES, THE SECOND OBTAINED AFTER QUICKLY RAISING CUFF PRESSURE BY 10 TO 15 MM. OF MERCURY IMMEDIATELY AFTER FIRST DIASTOLIC READING. BASED ON FORTY-ONE CASES WITH SUBJECT IN STANDING POSTURE

	FIRST READING (MM.)	SECOND READING (MM.)	DIFFERENCE (MM.)	CHANGE (%)
Arm	81	84	+3	+3.7
Thigh	155	164	+9	+5.8

STUDY 3

This study consisted in noting whether the diastolic pressure was significantly altered as a result of quiet standing for three minutes. Comparisons were made between the diastolic pressure in the thigh while it was horizontal, before and after the subject had stood for three minutes.

Results.—The mean results in thirty-three cases are revealed in Table III. Thus, standing for three minutes apparently did not have much effect on the mean blood pressure in the thigh in the entire group when readings were taken subsequently in the horizontal position. However, it must be realized that individual patients may show wide differences in the change in blood pressure which results from a change in posture. For example, there were differences of as much as a 30 mm. increase, or as much as a 34 mm. decrease, in the diastolic pressure in the horizontal posture after standing, compared to that before standing for three minutes.

TABLE III

COMPARISON OF DIFFERENCE IN BLOOD PRESSURE BETWEEN THIGH AND ARM IN HORIZONTAL POSTURE BEFORE AND AFTER STANDING FOR THREE MINUTES

	INCREASE (+) OR DECREASE (−) IN BLOOD PRESSURE DIFFERENCE, MM. OF MERCURY						
	CASE	AVERAGE DIFFERENCE AFTER STANDING		RANGE OF DIFFERENCE AFTER STANDING			
				1 MIN.		3 MIN.	
		1 MIN.	3 MIN.	MAX.	MIN.	MAX.	MIN.
Systolic	33	+4	−0.2	+42	−16	+32	−32
Diastolic	33	+2	−1.0	+30	−34	+30	−30

COMMENT

This study does not explain why some persons exhibit a considerable increase in diastolic pressure, whereas others show little or no change as a result of congestion. It does, however, indicate that such differences do exist, and that considerable differences may be found from person to person. The increase in diastolic pressure in response to congestion appears to be greater in the congested leg than in the congested arm.

We have gained the impression, which has not been proved, that those persons who have soft, flabby muscles, or who have been in bed for some time and who are in poor general condition, are prone to exhibit a greater increase in diastolic pressure and a greater tendency to a decrease in the intensity and clarity of the diastolic auscultatory sounds during congestion of the limb than do persons of the opposite type. It may be that venous tone and the venopressor mechanism[2] are more effective among those who have hard, muscular limbs, thus counteracting the tendency to venous engorgement.

Interestingly, the systolic pressure responds little or not at all to congestion. This suggests the possibility that the increase in diastolic pressure under such circumstances may be due to increased local arterial constriction in response to increases of venous pressure in the venous reservoirs. If the vessels of these reservoirs can increase their tone sufficiently, and if other factors constituting the venopressor mechanism can function effectively, venous return may not be much hampered. The venous reservoirs would be less engorged, so that the load distal to the arterial side of the vascular segment would be less. The arteries proximal to these reservoirs, which are subjected to less internal pressure, would tend to contract to a lesser degree. This might tend to lower the diastolic pressure. On the other hand, if the ability to increase venous tone in response to venous engorgement is defective, then the great venous reservoirs which are engorged as a result of the cuff which is obstructing venous return cannot empty themselves effectively. The increased venous pressure is transmitted backward toward the arterial portion of the circulation. To overcome this increased load and to restore the former arteriovenous gradient in pressure, there may be a rise of pressure in the arterial segments. Since systolic pressure does not increase much under these circumstances, the increase in diastolic pressure may be produced largely by local arterial constriction, rather than by an increase of cardiac output.

Defective arterial constriction in response to venous engorgement could be a factor in the failure of the diastolic pressure to increase in some persons during venous engorgement. However, one must also consider the possibility that such persons may have a highly effective venopressor mechanism, which would tend to counteract congesting influences. Such persons possibly can deal adequately with the extravascular burden at its very origin, with the result that little or no extra pressure is called forth in the arterial side of the circulation to maintain the proper arteriovenous gradient of pressure. These suggestions are offered merely as possibilities, evaluation of which would be quite difficult.

We believe this study indicates the desirability, when one is measuring blood pressure, of deflating the cuff as rapidly as possible, in order to obviate the error of relatively higher diastolic pressure which may result from slow or intermittent deflation of the cuff. If the level of diastolic pressure cannot be readily established at the initial deflation of the cuff, it would seem best to deflate the cuff completely, wait a few seconds, and then try again. Lewis[3] observed that, if the pressure in the cuff placed around a limb is raised in increments, the pressure in the veins distal to the cuff increases within a few seconds to the level of each new pressure induced within the cuff. The venous pressure could be increased in this manner to approximately the level of the arterial pressure. It may be that persons who fail to exhibit increases of diastolic pressure in the presence of venous engorgement within the limb are able to compensate adequately for such engorgement.

SUMMARY

The production of congestion of an extremity by means of a tight cuff usually results in little change in systolic blood pressure, but, in some cases, it may result in considerable increase in diastolic pressure and a decrease in the intensity of the diastolic auscultatory sounds in that extremity. It is not known why some persons exhibit these tendencies, whereas others do not. Possible mechanisms are discussed.

Slow or intermittent deflation of a blood pressure cuff below the level of systolic pressure may tend to increase the value of the diastolic blood pressure in some cases. Suggestions are offered to obviate this tendency.

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BLOOD PRESSURE IN THE ARM AND THIGH OF MAN

IV. Blood Pressure in Exercised Extremities

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AFTER we had observed the effect of congestion on the blood pressure in the arm and leg,[1] it seemed desirable to learn what effect exercise, by supposedly reducing venous engorgement, would have on the blood pressure. To observe the effects of exercise, subjects, while standing, were requested to rise up and down on the toes ten times during a period of ten to fifteen seconds. At the end of the eighth excursion the pressure within the pressure cuff around the thigh just above the knee was quickly inflated to a point above the level of systolic blood pressure; then, at the end of the tenth excursion, the subject remained as still as possible while the cuff was rapidly deflated. The blood pressure was measured by the cuff as it was being deflated. A second blood pressure measurement was made in this thigh one minute after the first, and, in some instances, a third reading was made three minutes after the first. These values were compared with the control blood pressures in the standing posture. Thirty-six of the 112 cases reported elsewhere[1] were studied in this manner.

Table I

The Effect of Exercise on the Blood Pressure in the Thigh, Standing Posture (Raising Up and Down on Toes for Ten Times in 10 to 15 Seconds). Based on Thirty-Six Subjects

	Control (mm.)	At end of exercise (mm.)	1 minute after exercise (mm.)	Change due to exercise (mm.)	Change (%)	Recovery in 1 minute (%)
Systolic	195	192	196	− 3	− 1.5	133.0
Diastolic	156	133	150	−23	−14.7	73.9

The major effect of such exercise was a considerable reduction in the diastolic blood pressure; the average reduction was 23 mm. of mercury (Table I). Whereas one minute after exercise there was an overshooting of the systolic blood pressure above the level prior to exercise, there was, during this time, recovery of only 74 per cent of the loss of diastolic pressure that had been produced by exercise. These points are illustrated in Fig. 1.

At first it was felt that the reason for the decrease in diastolic blood pressure after exercise might be an emptying of the venous reservoirs

Division of Medicine, Mayo Clinic.
Received for publication Jan. 25, 1944.

due to the exercise. If this were entirely true, exercising the leg while the cuff was inflated to a point well above the level of venous pressure would be expected to obviate much of this fall in pressure. To test this idea, twenty-six subjects were exercised with and without the cuff inflated to a point between systolic and diastolic blood pressure (Table II). There was essentially no difference in the two experiments in the change which occurred in the systolic pressure, and not much difference in the change which occurred in diastolic pressure, although the decrease in diastolic blood pressure was definitely less when venous return in the thigh was prevented by use of the tight cuff during exercise. Theoretically, the venous reservoirs of the exercised legs could not be emptied because of the obstructing cuff. Obviously, other factors were concerned in the reduction of the diastolic pressure which followed exercise. This reduction, it should be emphasized, was quite evanescent, for, in most cases, the diastolic blood pressure was back nearly to normal within a minute or so after the subject ceased exercise.

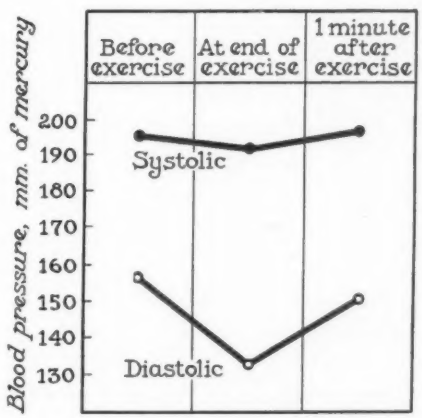

Fig. 1.—The effect of exercise of the legs (raising up and down on toes ten times in ten to fifteen seconds) on blood pressure in the leg while standing. Based on thirty-six subjects.

It is quite possible that such exercise reduces vascular tonus in the vessels of the extremity, perhaps by liberation of vasodilator substances or by reflex influences, or both. According to Anrep,[2] many substances associated with metabolism may produce vasodilatation. These influences include excess of carbon dioxide, histamine, and deficiency of oxygen. By the use of the hot-wire anemometer, Anrep showed that, during active exercise, there were a decrease of arterial inflow and an increase of venous outflow in the muscles which were being exercised. During relaxation these changes were reversed. In our studies the lowered diastolic pressure which was noted early in the relaxation which followed exercise may be related to relatively greater emptiness of the venous reservoirs produced by the muscular movements of exercise.

TABLE II

COMPARATIVE EFFECTS ON BLOOD PRESSURE IN THIGH IN STANDING POSTURE OF EXERCISE WITHOUT AND WITH THIGH CUFF HELD BETWEEN SYSTOLIC AND DIASTOLIC PRESSURES. BASED ON TWENTY-SIX CASES. (EXERCISE CONSISTED OF RAISING UP AND DOWN ON TOES TEN TIMES IN 10 TO 15 SECONDS)

	THIGH BLOOD PRESSURE			CHANGE (MM.)		CHANGE (%)	
	CONTROL (MM.)	WITHOUT CUFF (MM.)	WITH CUFF (MM.)	WITHOUT CUFF	WITH CUFF	WITHOUT CUFF	WITH CUFF
Systolic	194	191	190	− 3	− 4	− 1.5	− 2.1
Diastolic	155	134	139	−23	−16	−13.5	−10.3

During this investigation it was observed that, while a blood pressure reading was being obtained in the thigh while the subject was standing immediately at the end of exercise, or during deflation of a cuff which had been kept inflated for one to three minutes above systolic blood pressure in the thigh, there was a loud, soft, fairly continuous, blowing, systolic bruit which first became audible at the level of the diastolic blood pressure and lasted 15 to 20 mm. below that level. This bruit, although continuous, was accentuated during passage of the systolic impulse along the artery. This bruit generally was absent when the cuff was reinflated thirty to sixty seconds after the initial deflation. It was often noted that an indefinite and faint diastolic pressure sound in the thigh could be made more definite and louder by exercising the leg for a few seconds.

One can best explain the aforementioned bruit by reasoning that blood coming from a region of constricted vessels which have good tone passes by the cuff abruptly into a region whose vessels presumably are comparatively relaxed and dilated, and more capacious as the result of exercise. The transient effect of any vasodilator substances or of reflex vasodilator mechanisms in producing decreases of vasomotor tonus is quickly replaced by vasoconstriction as the abrupt inflow of blood into the leg during relaxation of the muscles and deflation of the cuff results in an increase of the internal vascular stretching force. In this connection one is reminded of the observations of Bayliss[3] that arteries tend to relax when pressure within them is decreased and to constrict when this pressure is increased.

SUMMARY

Exercise of the legs resulted in a transient, but considerable, reduction in the diastolic blood pressure in the leg, but little reduction in the systolic blood pressure. The average reduction in the diastolic pressure was 23 millimeters. The systolic blood pressure was reduced, on the average, only 3 millimeters.

The prevention of venous return by means of a tight cuff about the thigh while it was being exercised had only a slight effect in preventing the decrease of diastolic pressure in the leg.

Other factors besides emptying of the venous reservoirs must be responsible for the decrease of diastolic pressure in the thighs which is noted soon after they are exercised. Certain vasodilator substances produced in the exercised extremity may play a role in such reductions of blood pressure.

A soft, continuous, blowing murmur, accentuated during passage of the systolic wave along the arteries, was often heard as blood pressure was being measured within the first few seconds after cessation of exercise, or while a cuff which had been kept inflated above the level of systolic blood pressure for a few minutes was being deflated.

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THE EFFECT OF RENAL VEIN OCCLUSION ON THE BLOOD PRESSURE OF THE DOG

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SINCE the evolution of the Goldblatt method[1] of producing hypertension by partial renal artery constriction, other experimental methods of interference with the renal blood flow have been used to affect the blood pressure. Page[2] has shown that envelopment of the kidney in a cellophane membrane leads to hypertension by virtue of perinephritis. Another method used for the production of hypertension is that of ureteral obstruction.[3] In this condition, as a result of resistance to urine flow, the pressure within the nephrons rises, the rise is transmitted through the kidney by virtue of the relative rigidity of the kidney capsule, and interference with renal blood flow ensues. However, the latter experiments have resulted in either transitory hypertension, with early death in uremia, or a mild, longer lasting blood pressure rise.[3] Still another experimental procedure has employed constriction of the renal vein. Such constriction, by obstructing outflow, interferes with the normal rate of blood flow through the kidney. Bell and Pedersen[4] succeeded in producing hypertension of about two months' duration in the rabbit by partial occlusion of the renal vein and placing a membrane around the kidney to prevent development of the rich venous collateral circulation which is known to follow renal vein occlusion. Dicker[5] and Braun-Menéndez[6] were successful in producing a slight pressure rise in the dog by partial venous occlusion alone, but this was transitory. A case of hypertension in a 12-year-old boy which was apparently due to occlusion of one renal vein by a thrombus has been reported by Perry and Taylor.[7]

The present study was undertaken in the endeavor to produce longer lasting hypertension by renal vein occlusion. For this purpose, in the long-term experiments, an attempt was made to apply enough constriction to prevent, if possible, early compensation by collaterals, and yet not to occlude enough to lead to progressive and fatal renal excretory insufficiency.

Since this type of interference with renal blood flow differs basically from the other types described above, pathologic studies of the kidneys were made to ascertain the effect of a long-standing increase of pressure within the organ upon the structure of the renal vessels.

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Aided by the A. D. Nast Fund for Cardiovascular Research. The department is supported in part by the Michael Reese Research Foundation.

Received for publication Feb. 17, 1944.

METHODS

Blood pressures were measured with the Hamilton needle manometer.[8] The dogs were trained preoperatively, as previously described,[9] until control diastolic blood pressures showed variations of not more than ± 5 mm. Hg. Blood nonprotein nitrogen determinations were carried out by the method of Koch.[10] The operations were performed under sterile conditions on dogs anesthetized with nembutal or ether. In most cases the ligature method of Drury[11] was employed in partially constricting the veins. In some, a silver band, 2 mm. wide, was used for constriction. The venous occlusion was carried out bilaterally, or, more often, unilaterally, combined with contralateral nephrectomy either preceding or immediately following the venous occlusion. In the reoperations, carried out under similar anesthesia, visible collateral veins were ligated.

RESULTS

1. *Complete Occlusion of Both Renal Veins.*—Preliminary observations were made on bilateral, complete, venous occlusion in sixteen animals. All of these animals succumbed in from one to five days, with evidence of uremia. None showed hypertension. The kidneys at necropsy were intensely engorged; often, the renal capsule was ruptured, and in these cases there was extensive extrarenal hemorrhage.

2. *Partial Constriction of the Renal Vein.*—Bilateral, partial, venous occlusion was done in two experiments, and unilateral partial renal vein occlusion, with contralateral nephrectomy, in sixteen experiments. In eight animals, no blood pressure elevation was observed, although in five of these the nonprotein nitrogen rose temporarily to a varying extent. In the remaining eight animals a slight to moderate, immediate blood pressure rise resulted, reaching hypertensive levels in all. Three of the positive experiments are shown in Figs. 1, 2, and 3. The blood pressure rose immediately (within twenty-four hours) in all but one case, in which the rise began after a three-day lag. The pressure rise lasted from two to eight days. In only two instances was it accompanied by a rise in nonprotein nitrogen; in the other six the nonprotein nitrogen remained at its normal level.

In six instances the blood pressure returned to normal. In the other two instances, the pressure continued elevated to a moderate extent, but showed fluctuation. In Y 118 (Fig. 1), this later elevation persisted for 734 days and through two pregnancies. In Y 135 (Fig. 2), the blood pressure elevation lasted 60 days, until reoperation. In one of the dogs in which the renal vein was bilaterally occluded (X-5), one of the kidneys was removed 60 days later, and this was followed by elevation of the blood pressure for 39 days, when the experiment was interrupted by constricting the renal artery of this kidney for another experiment. As expected, a more marked hypertension occurred after the arterial constriction.

3. *The Effect of Reoperation to Reduce the Collateral Venous Supply of the Kidney.*—It soon became apparent from post-mortem examination

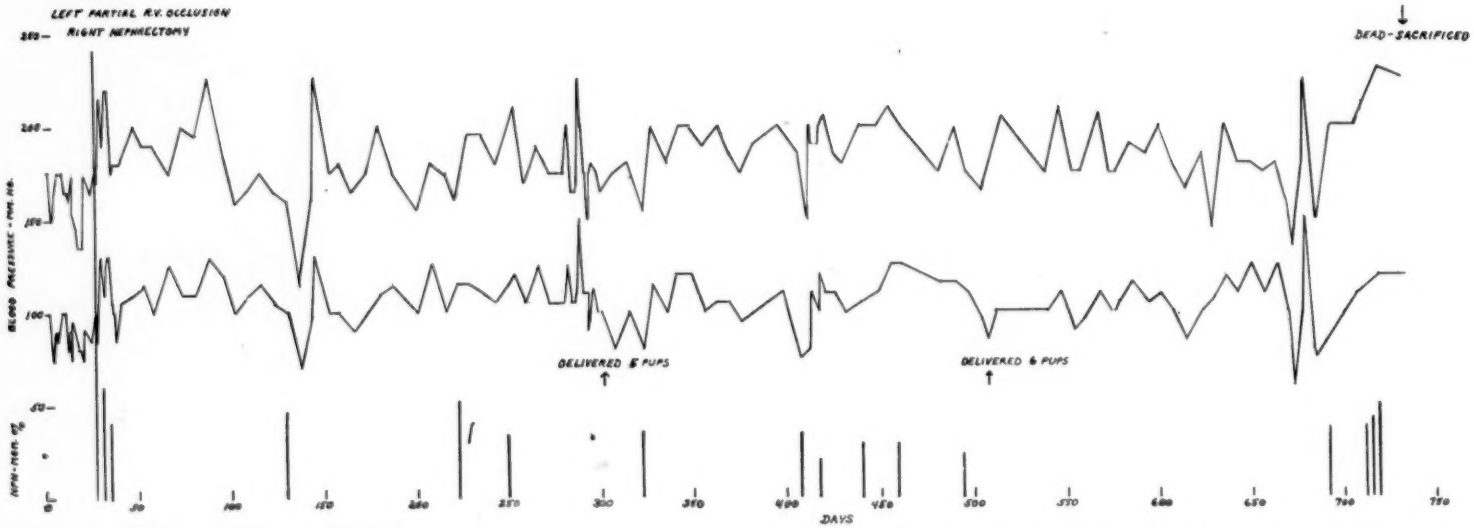

Fig. 1.—Blood pressure and nonprotein nitrogen in a dog (Y 118) which developed long standing, fluctuating hypertension after partial unilateral renal vein occlusion and contralateral nephrectomy. Top line represents systolic blood pressure, lower line diastolic blood pressure, columns at bottom, blood nonprotein nitrogen level. This animal went through two pregnancies during the course of the experiment. Time of parturition is indicated by arrows. RV = renal vein.

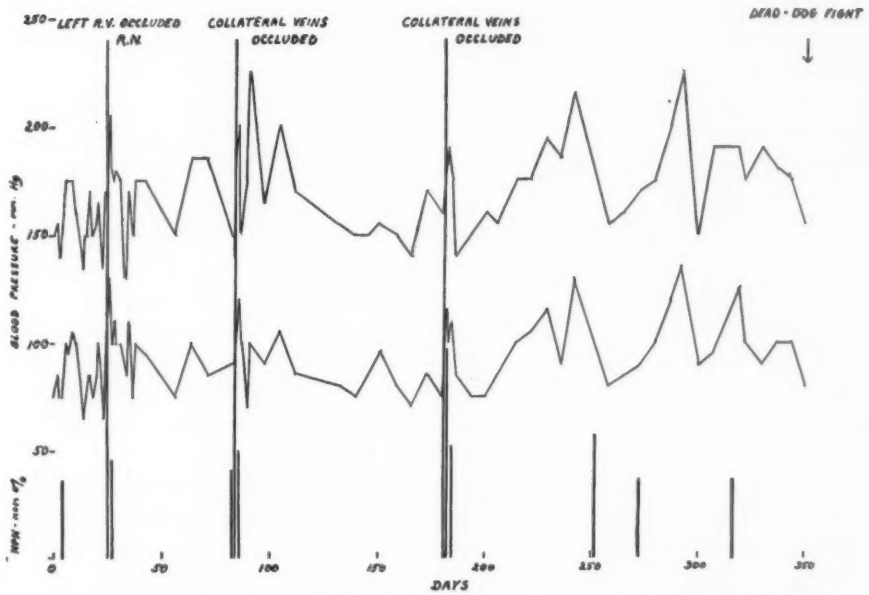

Fig. 2.—Blood pressure and nonprotein nitrogen in a dog (Y 135), showing the effect of unilateral renal vein constriction and contralateral nephrectomy and the effect of occluding the collateral capsular veins on two occasions by reoperation. *R.V.* = renal vein; *R.N.* = right nephrectomy.

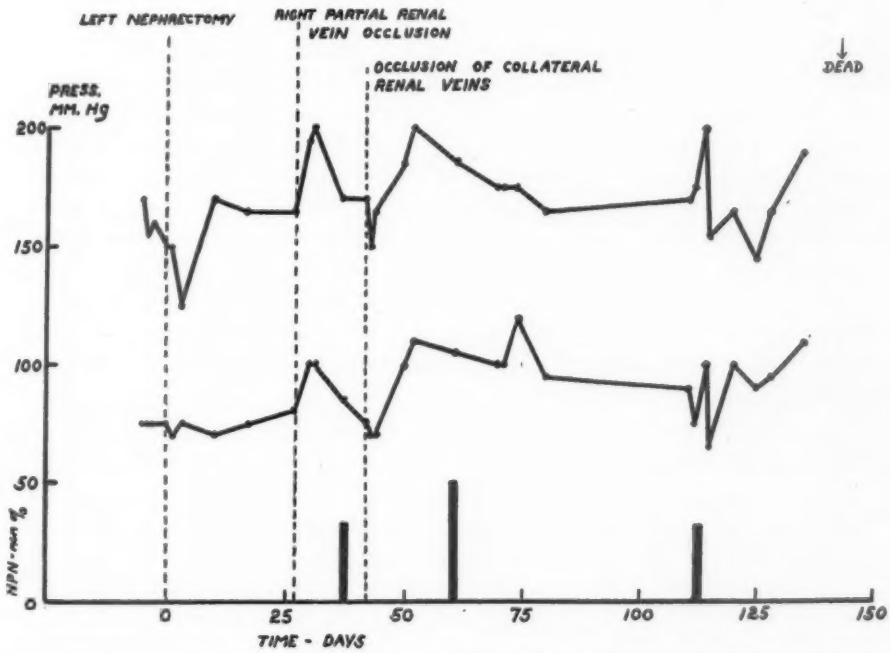

Fig. 3.—Blood pressure and nonprotein nitrogen in a dog (Y 32) after renal vein constriction of the remaining kidney and occlusion of the capsular collateral veins on reoperation.

of these kidneys that a very rich collateral venous network developed in the hilum and around the entire capsule. We reoperated on a number of these animals in an attempt to obliterate these collateral veins. Such reoperations were done once on four animals, without sustained hypertension after the initial venous occlusion, and twice on three animals, one with, and two without, sustained hypertension after the initial venous occlusion.

The first reoperation was done anywhere from 15 to 76 days after the initial operation. In four, neither transitory nor prolonged blood pressure elevation occurred. In the other three, an immediate blood pressure rise developed, lasting from two (Fig. 2) to ten days; in the latter this appeared after a seven-day lag (Fig. 3), but in the others the rise was immediate. In two of these animals, this immediate rise was succeeded by a later, fluctuating, moderate hypertension lasting 70 and 101 days, respectively.

Five animals were subjected to a second reoperation to obliterate the venous collaterals; this was done 75 to 278 days after the first reoperation, and three of these animals showed a transitory, immediate hypertension lasting one to three days (Fig. 2). In two, this was succeeded by a long lasting, fluctuating hypertension of moderate degree (176 [Fig. 2] and 400 days' duration, respectively).

Gross and microscopic examination of the kidneys was carried out.*

Grossly, there was a large amount of scar tissue around the site of ligation. Large collateral veins were abundantly distributed to the capsule and renal pelvis. The kidneys were bound down frequently by operative adhesions, which, in two instances of long standing hypertension (Y 32 and Y 118), actually distorted the shape of the kidney. In no instance was the renal artery found to be constricted or distorted by the scar tissue, and its lumen was widely patent and free of thromboses in every case. The kidneys were found to be somewhat paler than normal, but the blood vessels were more clearly evident than usual.

Microscopically there was evidence of chronic passive congestion, with the blood vessels widely dilated and engorged. The connective tissue was slightly increased and the tubular epithelium showed various degrees of cloudy swelling. No significant changes in the glomeruli were noted. Slight thickening of Bowman's capsule was observed occasionally. Small focal hemorrhages, with foci of lymphocytic infiltration, were also present. No significant changes in the renal arteries, arterioles, or veins were noted in any case, even in those animals which exhibited the longest and most marked hypertension.

DISCUSSION

It is clear from these results that, when the obstruction to renal venous flow is too great, as with complete occlusion of both renal veins, progres-

*The microscopic examinations were checked by Dr. O. Saphir, head of the Department of Pathology.

sive renal excretory insufficiency develops and the animal dies of uremia. Apparently the flow from the kidney is so impaired in this condition that the amount of the humoral mediator of hypertension which enters the blood stream is insufficient to cause any change in blood pressure. Such renal impairment, with no elevation in blood pressure, again illustrates the discrete relationship between hypertension and renal excretory insufficiency.[12] When the obstruction is too slight, however, not enough interference occurs in renal blood flow to initiate the production of a sufficient amount of the humoral mediator of hypertension to cause a blood pressure change. Unilateral obstruction, intermediate in degree, when accompanied by contralateral nephrectomy, produces at least temporary hypertension. This is accompanied by a mild, transitory impairment of renal function. The disappearance of the hypertension and azotemia is apparently due to the development of a rich venous collateral circulation, opened up by the elevation of renal venous pressure. Such venous collateral formation may occur more rapidly than collateral renal arterial supply, and may help to explain the more transitory nature of this type of hypertension. The speed and degree of collateral vein formation vary considerably from dog to dog. The effect of the collateral circulation can be retarded by operative ligation, in one or two stages, of the venous channels which develop, thus increasing the possibilities of producing a longer lasting hypertension.

Thus, hypertension lasting 734, 101, 70, 39, and 400 days, respectively, was produced in five dogs. In a sixth dog (Fig. 2), hypertension for 60 days, followed by an interval of 98 days of normal blood pressure and another period of hypertension of 176 days, occurred. However, these repeated operative procedures increase the chances of the development of a secondary connective tissue proliferation around the kidney.[13] By its contraction, this process acts in a manner similar to the perinephritis which follows envelopment of the kidney by a membrane. In fact, it has been shown that the attempt to increase the blood supply to the kidney by myopexy is ineffective in preventing hypertension for the same reason, i.e., capsular scar tissue formation, with compression.[13] In view of the multiplicity of factors involved, variability in results of such experiments are therefore not unexpected.

It has been established that essential hypertension in man often is associated with renal arteriolosclerosis.[14] Occasionally, however, renal biopsies in cases with human essential hypertension fail to reveal these lesions.[15] However, these renal vascular lesions have not been found in long standing, experimental renal hypertension, whether produced by renal artery occlusion[16] or by perinephritis.[17] The absence of renal arteriosclerosis in the former has been explained by the fact that the constriction of the renal artery prevents the hypertension from appearing in the renal arterioles. If the perinephritis occludes the main renal artery at the hilum or smaller arteries of the cortex, the same explana-

tion would apply. The absence of arterial change might have a similar explanation in our experiments with renal vein occlusion, for perinephritis occurs. This, if it is the explanation, must have involved the smaller cortical vessels, for the main renal artery was found unobstructed at necropsy. Further, resistance of species may play a role, for Goldblatt[18] has been unable to find arteriosclerosis anywhere in the body of the dog, except the eyeball, after long standing hypertension resulting from renal artery constriction. Thus it might well be that the dog is not a suitable animal in which to induce arteriosclerosis by long standing blood pressure elevation. The results with chronic renal vein occlusion may be germane to the mechanism of the hypertension which sometimes develops during congestive heart failure. In congestive failure there is sometimes a protracted elevation of venous pressure which can affect the kidneys in much the same way as in these vein occlusion experiments. However, in congestive failure it is not possible to compensate for this by the development of collaterals because the venous pressure elevation is universal in the systemic circuit. These experiments, therefore, may serve to account for one mechanism by which hypertension appears in congestive failure.

CONCLUSIONS

1. Complete bilateral obstruction of the renal vein leads to death in uremia, with suppression of renal function. No rise in blood pressure is observed.

2. Partial renal occlusion sometimes leads to mild, transitory hypertension which is soon dissipated by the formation of an extensive capsular venous network. In one dog, however, this procedure led to moderate, fluctuating hypertension which lasted over two years.

3. Reoperation and reocclusion of the collateral veins which develop is occasionally effective in producing a more severe and long lasting hypertension (of several months' duration). This may be due to effective interference with the venous drainage of the kidney, or to compression of the kidney by the scar tissue around the hilum and capsule which follows reoperation.

4. No permanent vascular changes were found in the kidney which might be related to arteriosclerosis, even in those animals with the more severe and longer lasting hypertension.

I am indebted to Dr. L. N. Katz for guidance in the pursuit of this problem.

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MOMENTARY ATRIAL ELECTRICAL AXES

I. Normal Sinus Rhythm

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THIS paper describes a method of study of the atrial electrical impulse which may be used on persons who have normal hearts, or on patients who have abnormalities in the size, shape, or position of the heart, or of the site of impulse generation. Results obtained under abnormal circumstances will be reported later.

In 1921, Lewis, Drury, and Iliescu[1] employed simultaneous chest leads in an effort to demonstrate, on patients, the presence of a circus movement in atrial flutter and fibrillation. Their clinical data appeared to substantiate the conclusions which they had derived from preceding animal work. Lewis placed his leads on the chest wall in such a fashion that the electrical axis of the atrium could be measured from moment to moment in the sagittal, horizontal, and frontal planes. The electrical axes and the manifest electrical potential at each moment were calculated by means of the Einthoven triangle, and, from the data obtained from each plane, a three-dimensional circus movement was postulated for flutter, and an irregular, variable circus pathway for atrial fibrillation.

Our facilities did not permit us to take three simultaneous leads as Lewis, et al., did. We have, however, duplicated as nearly as possible their procedure, and have taken two leads simultaneously in each of the three planes by means of the Sanborn Tri-Beam Stetho-Cardiette. Each pair of leads may be taken simultaneously, i.e., Leads I and II, II and III, and I and III, and, by careful projection and matching, the three leads may be traced as though they had been taken simultaneously.

METHOD OF STUDY

In the *sagittal* plane, curves were taken by placing the right arm electrode over the manubrium, the left arm electrode over the xiphoid, and the left leg electrode on the back just to the right of the seventh dorsal spine. In the *horizontal* plane, the right arm electrode was in the left fifth intercostal space, near the left nipple, the left arm electrode in a corresponding position on the right side of the chest, and the left leg electrode on the back in the position mentioned above. The *frontal* projections were obtained by switching the left leg electrode from the back to the position over the manubrium sterni. The limb leads do not give a true frontal plane projection, as has been

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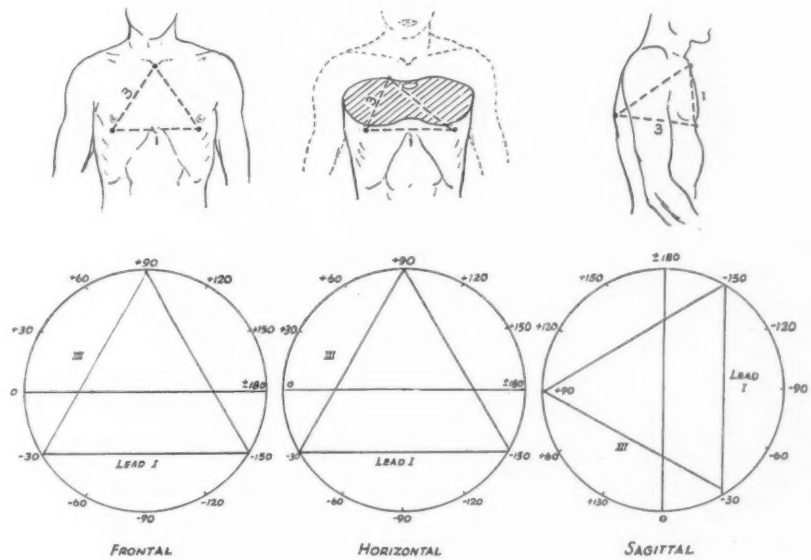
Received for publication Feb. 21, 1944.

pointed out by Schellong.[2] The appropriate position of the Einthoven triangle that is formed when the electrodes are thus applied is shown for each plane in Fig. 1. With the Sanborn instrument simultaneous leads were recorded: Leads I and II, II and III, and I and III. We were careful to place the electrodes so that the triangle formed was as nearly equilateral as possible. The tracings obtained were placed in an opaque projector, and were thrown, enlarged ten times, upon a piece of graph paper. They were traced on this graph paper, and the enlarged tracing was utilized for the measurements necessary to ascertain the electrical axis and the manifest potential, using the method of Carter, Richter, and Greene.[3]



POSITION OF THE EINTHOVEN TRIANGLES IN THE 3 PLANES

Fig. 1.—*A*, Position of the electrodes, and the triangle formed in the three planes: frontal, horizontal, and sagittal. *B*, The position of the Einthoven triangles, and their angles, in the three planes.

The electrical axis calculated for each 0.01 second was plotted as shown in Fig. 2. It was assumed that the wave of depolarization travels a unit distance per 0.01 second, and the direction of the vector derived for each moment was plotted, beginning with the termination of the vector for the preceding time interval. The line thus obtained represents the consecutive momentary atrial electrical axes, and may be drawn for each of the three planes. By utilizing all three of the curves thus derived, one may visualize in three dimensions the momentary shift in the atrial electrical axis. The figures thus drawn or visualized have, of course, an anatomic basis, but are related only indirectly to the actual pathway of the electrical wave as it traverses the atrium.

Fig. 1 shows diagrammatically the details of the position of the electrodes on the chest wall. It illustrates the facts that (1) the triangles formed were usually not perfectly equilateral; (2) the plane designated as horizontal actually slanted down and forward; and (3) the posterior portion of the sagittal plane was slightly to the right of the midline. Fig. 2 shows the simultaneous records of Leads I and III in each plane, as derived from a normal young man. Below these tracings are graphed for each plane the consecutive electrical axes for each 0.01 second. In this case the atrial electrical activity lasted 0.11 second.

The curves for the frontal and horizontal planes show reasonable agreement, indicating that during the first 0.05 to 0.06 second the curve progressed forward and downward; later the axes inscribed a curve pointing to the left and downward. In the sagittal plane the vectors representing the electrical axes curved forward and down for 0.04 second, and after this ran nearly straight down. The photograph represents an effort to depict these movements in a single three-dimensional figure. The shadows show the projections of the "actual" axes upon the frontal and sagittal planes, thus approximately reproducing the curves actually obtained from the electrocardiograms taken in these planes. The position of the camera does not quite permit visualization of the curve in the slanting horizontal plane.

It must be emphasized that each segment of the curve represents only direction and time. The magnitude of the manifest potential cannot be shown without additional pictorial features, such as variation in the width of the line, and it was felt that this would unnecessarily complicate the figures. The use of a unit segment for each time interval in each plane cannot take into account the fact that the planar diagrams are projections of the "actual" electrical axis, and hence could not be equivalent on each plane. For this reason, there will be discrepancies when the "actual" axis is deduced from its three projections. In spite of all these deficiencies, the general trend of direction of the electrical axis is readily apparent in each instance.

Data obtained in this fashion depend, for their absolute value, upon the validity of the hypothesis originally advanced by Einthoven. Experimental proof of the validity of Einthoven's triangle is lacking. Fahr,[4] in 1920, mentioned briefly the fact that he had performed experiments on cadavers which showed that the Einthoven triangle was accurate to within ±10 degrees. There is abundant evidence[5] that the hypothesis cannot be justified absolutely for the human heart, because of the fact that the heart is not in the center of an equilateral triangle, and that the electrical properties of the tissues concerned do not fulfill the hypothesis. In spite of the theoretical and practical objections to the use of the Einthoven triangle, it has served profitably for valuable clinical experimentation.

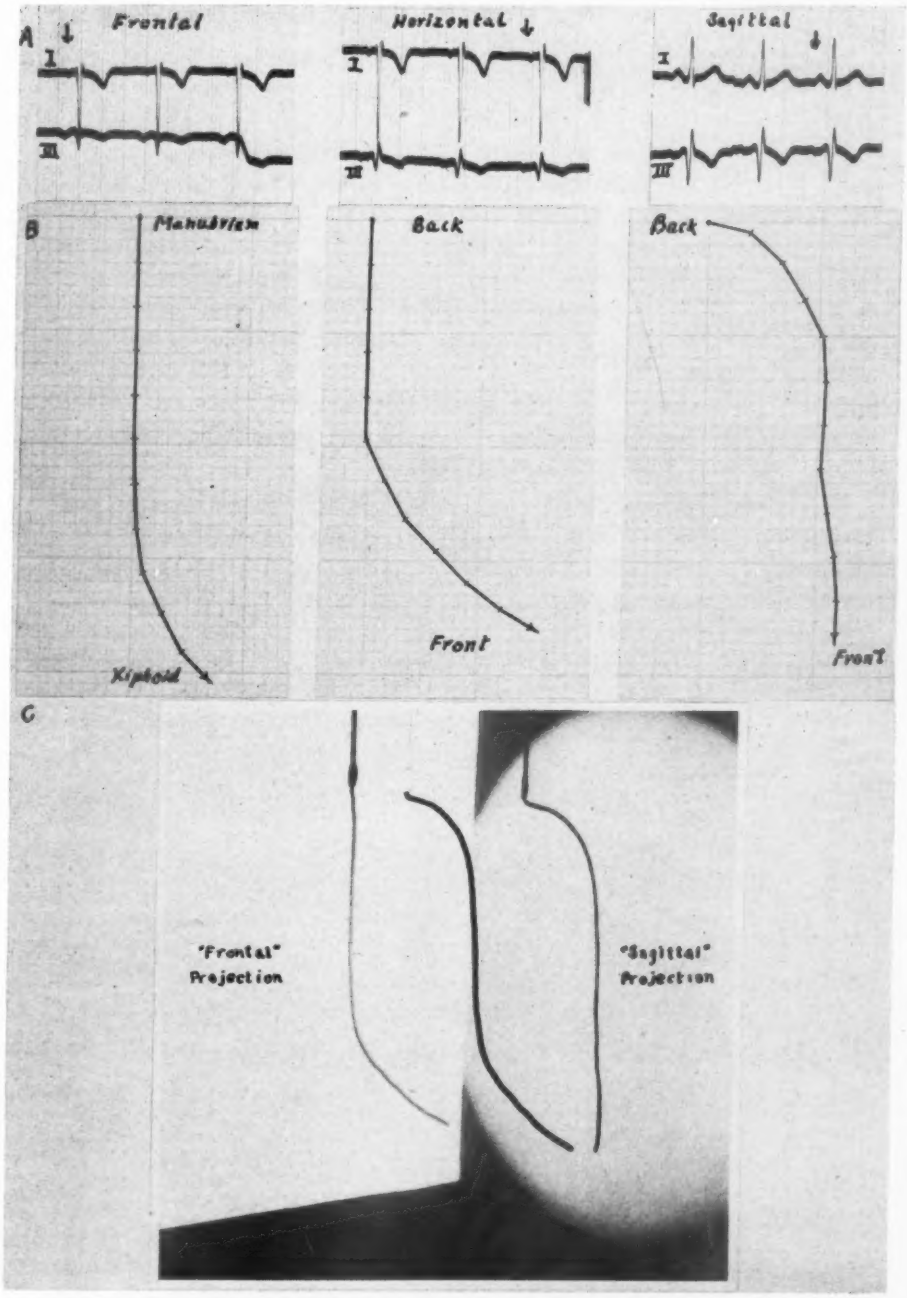


Fig. 2.—*A*, Simultaneously recorded Leads I and III for each plane, frontal on the left, horizontal in the middle, and sagittal on the right. *B*, Curves for each plane representing the direction of the atrial axes for each consecutive 0.01 second; see text. *C*, Photograph of a three-dimensional model in which the black wire represents the atrial axes. The shadows represent the projection on the frontal plane (left) and sagittal plane (right). They approximate the original curves for these two planes, shown above. The curve for the horizontal plane was utilized in arranging the position of the wire, but could not feasibly be reproduced by a third shadow.

Fig. 3 shows simultaneous tracings of the atrial complexes in Leads I and III, in each plane, taken on a normal male medical student. Lead II has been drawn in by carefully matching the projection of Leads II and III on the graph paper. For comparison, Lead II was calculated from the values for I and III, and is shown by the dotted line. The data employed are summarized in Table I. In the horizontal and frontal planes, the tracing drawn from the calculated data agrees quite well with Lead II as actually obtained. In the sagittal plane, however, there is considerable discrepancy. This has been found to be the case with other patients. Therefore, the curves derived from the sagittal plane are probably less accurate than are those in the other two planes. The ease with which the data from the three planes may usually be combined into a three-dimensional figure indicates to us that there is great practical usefulness in the Einthoven triangle hypothesis.

The theoretical aspects of vector analysis have been thoroughly discussed by Schellong[2] in his recent monograph. Weber[6] and Burger[7] made early studies of the momentary change of direction of the ventricular electrical axis. Mann[8] first attempted to derive a monocardio-

TABLE I

PLANE	TIME (SECONDS)	LEAD I	LEAD II		LEAD III	ANGLE (DEGREES)
			OBSERVED	CALCULATED		
Frontal	0.01	0.1	−0.3	−0.5	−0.6	− 82
	.02	0.2	−1.8	−1.8	−2.0	− 86
	.03	0.0	−2.8	−3.3	−3.3	− 90
	.04	−0.4	−4.8	−5.1	−4.7	− 94
	.05	−1.0	−7.6	−7.3	−6.3	− 98
	.06	−1.3	−8.2	−7.7	−6.4	−100
	.07	−2.0	−7.0	−8.0	−6.0	−105
	.08	−1.9	−4.7	−5.6	−3.7	−113
	.09	−1.8	−3.0	−4.0	−2.2	−117
	.10	−1.2	−1.5	−2.4	−1.2	−120
	.11	−0.5	−0.3	−1.0	−0.5	−120
Horizontal	0.01	0.2	−0.4	−0.4	−0.6	− 70
	.02	0.2	−1.4	−1.4	−1.6	− 83
	.03	0.3	−2.8	−2.6	−2.9	− 84
	.04	0.1	−3.8	−3.1	−3.2	− 88
	.05	−0.6	−4.1	−3.8	−3.2	− 98
	.06	−0.6	−4.0	−3.4	−2.8	− 99
	.07	−0.4	−3.4	−3.3	−2.9	− 97
	.08	−0.7	−2.7	−3.0	−2.3	−104
	.09	−0.2	−1.8	−1.5	−1.3	− 98
	.10	0.1	−0.9	−0.6	−0.7	− 97
	.11	0.1	0.0	−0.3	−0.4	−101
Sagittal	0.01	2.2	0.0	1.8	−0.4	20
	.02	3.8	0.6	2.5	−1.3	11
	.03	5.7	1.0	3.5	−2.2	5
	.04	8.3	0.8	4.6	−3.7	4
	.05	9.5	1.8	4.8	−4.7	0
	.06	9.4	4.0	3.9	−5.5	− 4
	.07	7.4	4.0	1.8	−5.6	− 13
	.08	5.4	3.5	0.4	−5.0	− 24
	.09	3.2	2.0	−0.4	−3.6	− 35
	.10	1.3	0.3	−1.0	−2.3	− 55
	.11	0.3	0.3	−0.4	−0.7	− 64

gram by calculation from the usual limb leads, and later devised an instrument whose beam was influenced by the potentials from all three leads.[9] Wilson and Johnston[10] employed the cathode-ray oscillograph for the same purpose. At about the same time, Schellong,[2] Hollmann and Hollmann,[11] and Guckes[12] began extensive clinical and experimental investigations of vector diagrams obtained from the human heart. These authors used differing leads and planes, but in each instance obtained tracings which represent the pathway, either in one plane or in three dimensions, of the ends of the momentary ventricular vectors of varying length, as the vectors rotate about a fixed point. Polar electrocardiograms were thus obtained instead of linear ones.

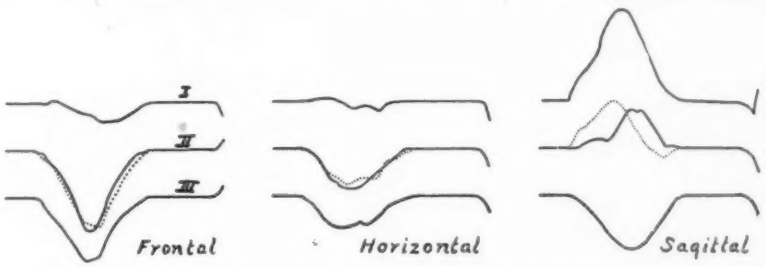


Fig. 3.—Reproduction of three leads in each plane, derived from a normal subject. Leads I and III were taken simultaneously, and traced upon graph paper. Leads II and III were superimposed by projection. The values of Lead II, as calculated from those of I and III, are shown by the dotted line. The data are in Table I.

By Mann's first method the vectors of the P wave may be satisfactorily measured. The methods which employ the oscillographic tube are valuable in studying the ventricular complexes, but yield such small complexes corresponding to the P wave that no conclusions may be derived from them. Our method of graphing differs, in that the electrical axis for each 0.01 second follows that for the preceding instant, rather than lying by its side. Our graph also differs from those employed by Lewis, although his data, when graphed by our method, give curves which are, in general, in agreement with ours.

EXPERIMENTAL RESULTS

Normal Persons.—The curve in Fig. 2 shows the momentary shifts in the atrial electrical axis in one normal person. Fig. 4 shows the models of six curves derived in a similar manner from normal male medical students. In the *frontal* plane most of the curves pass down and to the left in a rather uniform fashion. In one, however (Fig. 4, *f*), the curve moved to the right at an angle of −72° before turning down and towards the left; in this case fluoroscopic examination showed an unusually prominent right atrium, but no other indication of heart disease was detected. In the *horizontal* plane the curve forms an arc which moves forward and to the left, but with considerable variation. The early portion may point, as it did in one instance, slightly to the

right (–74°) before turning to the left; or the axes in the first few segments may point as much to the left as –140°. The terminal portion of the curve shows variation between –104° (forward and slightly to the left) and +160° (to the left and slightly backward). The curves obtained in the *sagittal* plane are consistent in that they usually move down, and, at first, forward; the terminal segments may turn, varying

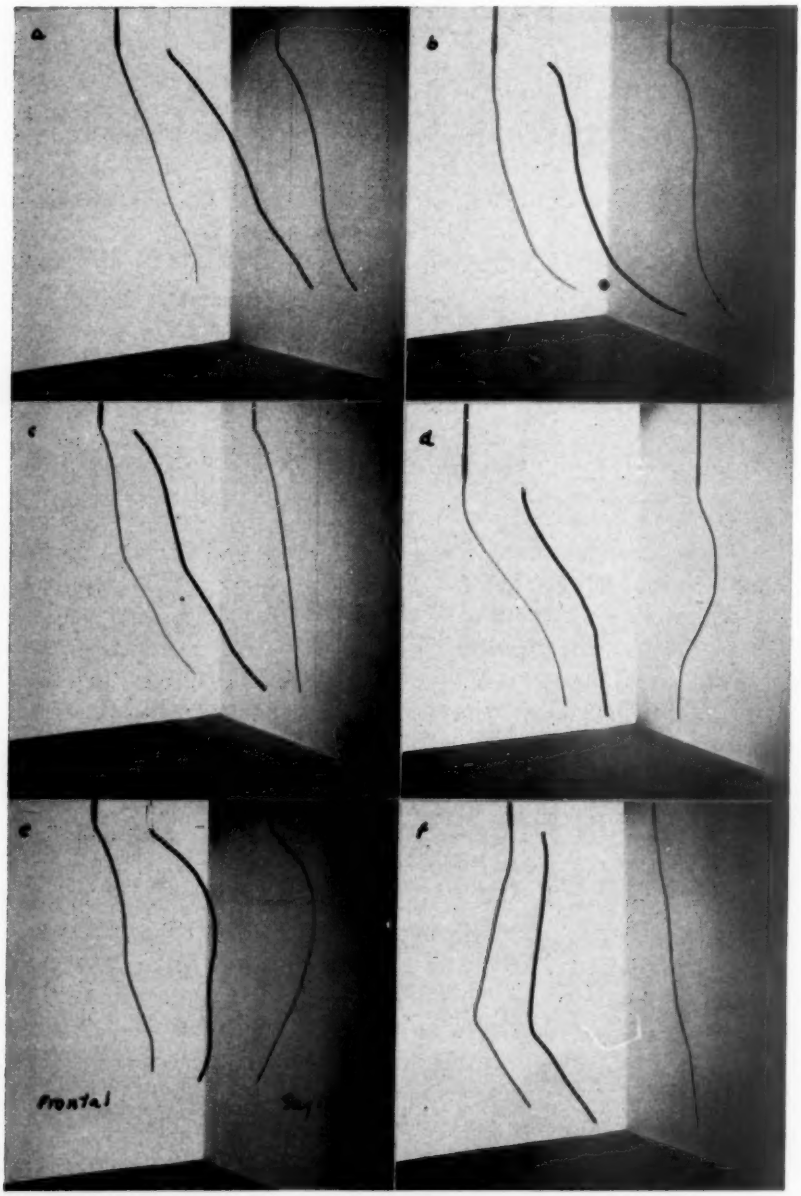


Fig. 4.—Atrial axes for consecutive 0.01 seconds, derived from normal young men, as described in the text and illustrated in Fig. 2.

from −90° (straight forward) to +30° (slightly backward). In one instance the curve in the sagittal plane showed a slight backward convexity. In general, normal persons appear to yield curves which are smooth and simple.

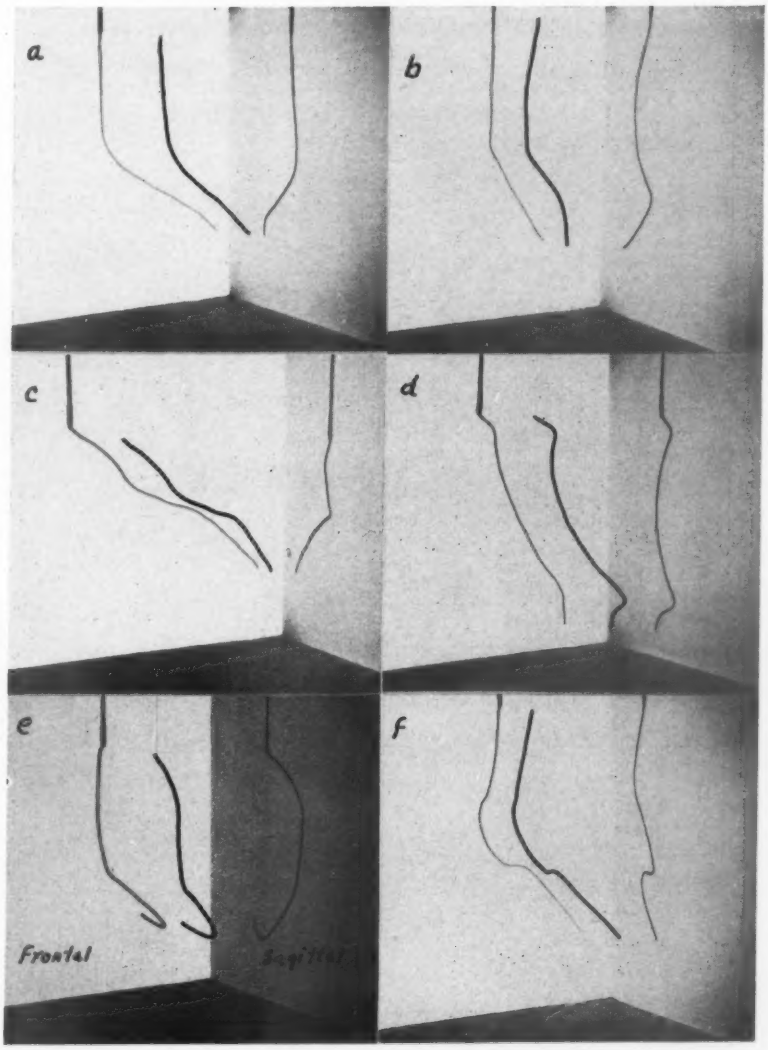


Fig. 5.—Consecutive atrial axes from patients with hypertensive and arteriosclerotic heart disease.

Patients With Heart Disease.—Fig. 5 shows six examples of the type of curve derived from patients with arteriosclerotic and hypertensive heart disease. The complexity of the curves fails to show, however, invariable correlation with the severity of the heart disease as judged by clinical standards. Thus, the curve in Fig. 5, *a*, is smooth, simple,

and devoid of complexity; it is the record of atrial activity in a case of hypertensive heart disease and congestive heart failure, with left bundle branch block and a QRS interval of 0.20 second. The curve in Fig. 5, *d*, is from a hypertensive patient with right bundle branch block of the Wilson type. The other tracings were derived from patients with clinical evidence of extensive myocardial disease. We regard the complexity of these curves, with their multiple changes in contour and

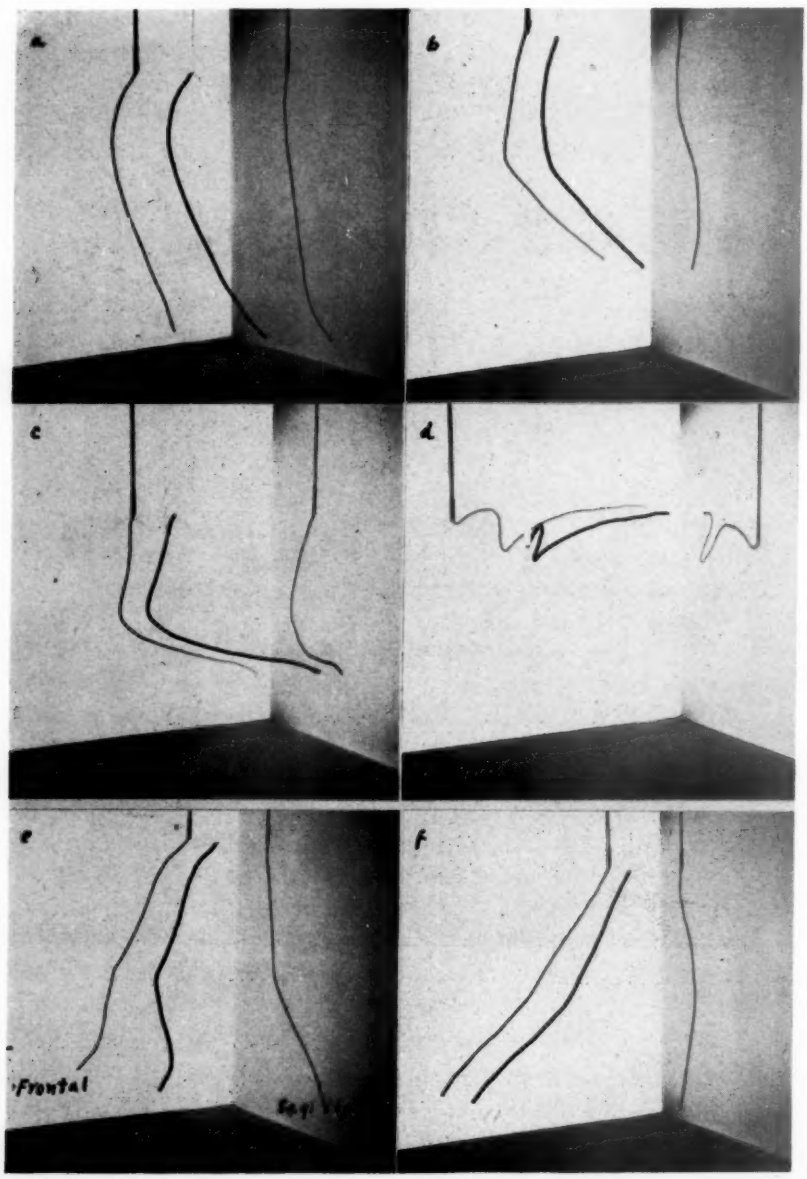


Fig. 6.—*a*, *b*, *c*, and *d*, Atrial axes in cases of mitral stenosis; see text. *e*, Dextroposition of the heart. *f*, Congenital dextrocardia.

direction, as a probable indication of disease of the atrial muscle, with conduction defects.

Two other types of anatomic abnormality are shown in Fig. 6. Fig. 6, *a*, *b*, *c*, and *d*, shows the curves from four patients with mitral stenosis. In Fig. 6, *a* and *b*, the curves move to the right and down, later turning to the left. Both patients had mitral stenosis of moderate grade. The curve in Fig. 6, *c*, is from a patient who had high-grade mitral stenosis, moderate aortic regurgitation, and congestive heart failure. Here the pattern of the two preceding curves is repeated in a more conspicuous manner. We suspect that this type of initial shift to the right of the atrial axes is to be connected with the dextroposition of the right atrium which occurs in such patients as a result of enlargement of the left atrium and the right ventricle. The patient from whom the curve in Fig. 6, *d*, was derived also had mitral stenosis and aortic regurgitation, but, in addition, had an acute exacerbation of rheumatic fever. We feel that disturbances in conduction through the atrial musculature, incident to acute rheumatic myocarditis, probably played a significant role in producing the bizarre curve obtained.

Dextroposition of an otherwise normal heart in a patient with extensive cystic disease of the left lung produced the changes illustrated in Fig. 6, *e*, in which the atrial axes move down, forward, and to the right. A similar but smoother curve was obtained (Fig. 6, *f*) from a young man with situs inversus and dextrocardia.

COMMENT

Presumably, the course of these curves is determined by the site of the pacemaker, and also by the physiologic and physical status of the atrial musculature. Anatomic circumstances make it reasonable to believe that the impulse originating in the sinoatrial node must spread down and to the left, and that the electrical axis, which is the resultant of the lines drawn perpendicular to the advancing wave of negativity or polarization, probably moves in a similar manner. Further study may make possible an exact correlation between the electrical axis and the electrically active portion of atrial muscle, similar to the analysis of the QRS complex made recently by Gardberg and Ashman.[13] However, it seems reasonable to anticipate that a change in the position of the pacemaker, a shift in the position of the heart, enlargement of one or both atria, and myocardial disease interfering with normal conduction will alter the curves of the electrical axes. Further study will be devoted to this, but, at this time, our interest is directed toward the general types of normal curves and their change of contour in certain disturbances of the atrial mechanism.

SUMMARY

Curves derived from patients with normal hearts show, in general, a shift of the consecutive atrial electrical axes down, forward, and to the left. The variations in this typical pathway are illustrated in Fig.

4, as well as one exception to this rule, in which there was a shift toward the right before the curve turned to the left.

Patients with myocardial disease may show a similar, smooth curve, or, more often, will yield curves which are complex, with multiple changes in direction and contour. Acute myocardial disease, as well as chronic myocarditis, may cause conduction defects which markedly alter the curve.

Patients with enlargement of other chambers of the heart which has pushed the right atrium toward the right, or, presumably, with enlargement of the right atrium itself, show curves which point to the right before turning to the left.

Dextroposition caused by disease in the lung or pleural space, or congenital dextrocardia, will produce curves which point entirely down and to the right.

Correlation of curves obtained by this method from persons with normal and diseased hearts with roentgenologic and necroscopic data is being undertaken. They are described at this time primarily for the purpose of setting up a standard for comparison with curves obtained from patients with atrial flutter, atrial fibrillation, and paroxysmal tachycardia, which are discussed in the second paper of this series.

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Clinical Reports

CHRONIC CONSTRICTIVE PERICARDITIS DUE TO A FOREIGN BODY (NEEDLE) IN THE PERICARDIUM

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CASES of constrictive pericarditis of traumatic origin are rare. Glenn[1] recently reported a case as a result of a crushing injury to the chest in an automobile accident. Warburg,[2] in an extensive review of the literature, cites three cases of traumatic origin, one of which was of dubious authenticity. Cases have been reported of bullets in the pericardium,[3] and migrating fish bones lodging in the pericardium, producing acute fibrinopurulent pericarditis.[4, 5] However, a review of the literature has failed to reveal any case of chronic constrictive pericarditis due to a foreign body. It is, therefore, believed that the following case of constrictive pericarditis caused by the lodgment of a surgical needle in the pericardium will be of interest.

REPORT OF CASE

T. B., a 46-year-old fireman, was admitted to the Veterans Hospital, Bronx, New York, June 23, 1942, with a diagnosis of "cirrhosis of the liver with possible obstruction." His chief complaint was that he had been losing weight since Christmas of 1941, but, despite that fact, his abdomen continued to be large and occasioned the ridicule of his fellow workers. He feared that he had an abdominal tumor, although he stated that he did not believe his abdomen had increased in size. In the preceding six months he had lost 30 pounds in weight. He complained of an excessive amount of gas, which was accompanied by belching. He had always been stout; his usual weight was 220 pounds. He had an uncomfortable sensation in his abdomen. When he walked rapidly, his "belly shook." In 1935, while fighting a fire, he fell three stories and sustained a fracture of the right knee, the left forearm, and several ribs on the left side. He was taken to a hospital, and, while undergoing an anesthetic preliminary to correction of the fractures, the patient stated that his heart stopped. He was given an injection in the third right intercostal space in the parasternal line. The needle broke off. An incision was made to recover the needle, but the attempt was unsuccessful. While in the hospital undergoing treatment for his fractures, he was told that pericardial effusion had developed. A physician wished to operate on his heart, but he was dissuaded against any operation by another physician. A roentgenogram in the patient's possession, taken in December, 1935, revealed evidence of pericardial effusion. The patient stated that, since the accident, his blood pressure had been low, usually about 88, systolic. He did not complain of shortness of breath or pain in the chest on admission. Seven years before

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Received for publication June 10, 1943.

he did have pain in the right side of his chest, but this disappeared completely. In December, 1941, he had an attack of phlebitis in the right leg, and still had occasional swelling of this extremity. He drank about three to four glasses of beer weekly. He never drank wine or hard liquor. This was confirmed by the patient's wife.

Examination disclosed a somewhat undernourished, well-developed, white male, with a protuberant abdomen, who did not appear to be acutely ill. His temperature was 98° F., his respirations, 20, and his weight, 188½ pounds. There was no dyspnea or cyanosis in the erect or sitting position. In the supine position, the patient's face and neck assumed a dusky, cyanotic hue. He did not become dyspneic. Examination of the fundi disclosed slight retinal arteriosclerosis. The veins of the neck were moderately distended in the erect position; in the supine position they were markedly so. The thorax was of medium size and configuration, and the lungs were normal. There was a 3 cm., linear, postoperative cicatrix in the third right intercostal space in the parasternal line. Heart: The point of maximum intensity of the apex impulse could not be palpated. The heart was not enlarged to percussion, the sounds were muffled, and the second sound was reduplicated at the apex. There were no thrills or murmurs. The blood pressure was 112/76-76. The pulse rate was 92. No appreciable peripheral arteriosclerosis was present. There was no paradoxical pulse, Broadbent's sign, or systolic retraction at the apex. The abdomen was swollen moderately. A fluid wave was present, and the liver was 1½ inches below the costal margin on the right. It was not tender. The spleen was not enlarged. There were no other masses. Extremities: The left arm was 2 inches shorter than the right. There was incomplete ankylosis at the elbow joint, and extension was limited to 165 degrees. Supination was moderately curtailed. There was a 4 by 3 cm. cicatrix over the right knee. Flexion of the right leg at the knee joint was limited to 90 degrees.

Laboratory studies: A roentgenogram of the chest (Fig. 1) on June 30, 1942, showed that the heart and lungs were within normal limits. There was evidence of a pleuropericardial adhesion at the base. Two linear densities were seen at the border of the pericardium at the right. These had the appearance of broken fragments of a needle. The roentgenologist said that they appeared to be embedded within the pericardium or myocardium. Fluoroscopic examination revealed marked diminution of the phasic excursions of the heart. The pulsations were feeble. There was no change in the heart size or position with deep inspiration or expiration. Esophageal study with barium showed no definite abnormalities. There was no evidence of esophageal varices. The electrocardiogram (Fig. 2) revealed a diphasic T_2; T_3 was inverted. QRS_3 was of low voltage, and S_3 was prominent. The venous pressure measurement, using the direct method, on July 3, 1942, was 33.5 cm. (normal, 4 to 12 cm.). On July 9 the venous pressure was 27.5 cm. The arm-to-tongue time on July 3, 1942, using sodium dehydrocholate, was 18 seconds (normal, 12 to 18 seconds). On July 9 the arm-to-tongue time was 10 seconds. The arm-to-lung time (ether) on July 3, 1942, was 6 seconds (normal, 4 to 6 seconds). Bromsulfalein test: 5 minutes, 85 per cent; 30 minutes, 5 per cent. The icteric index was 12.5. The van den Bergh was 0.1 mg. The serum albumin was 5.2, the serum globulin, 2.8. There was a mild anemia. Chemically, the blood was normal. The urine was negative. The blood Wassermann and Kahn reactions were negative.

Diagnoses of "chronic constrictive pericarditis of traumatic origin, with enlargement of the liver and ascites, Class III, and foreign body, metallic, right side of the chest" were made. The cause of the constrictive pericarditis was believed to be either the needle in the pericardium or the original trauma, i.e., the fall. Pericardiectomy was recommended. However, the patient wished some time to arrange his affairs, and he was discharged July 14, 1942.

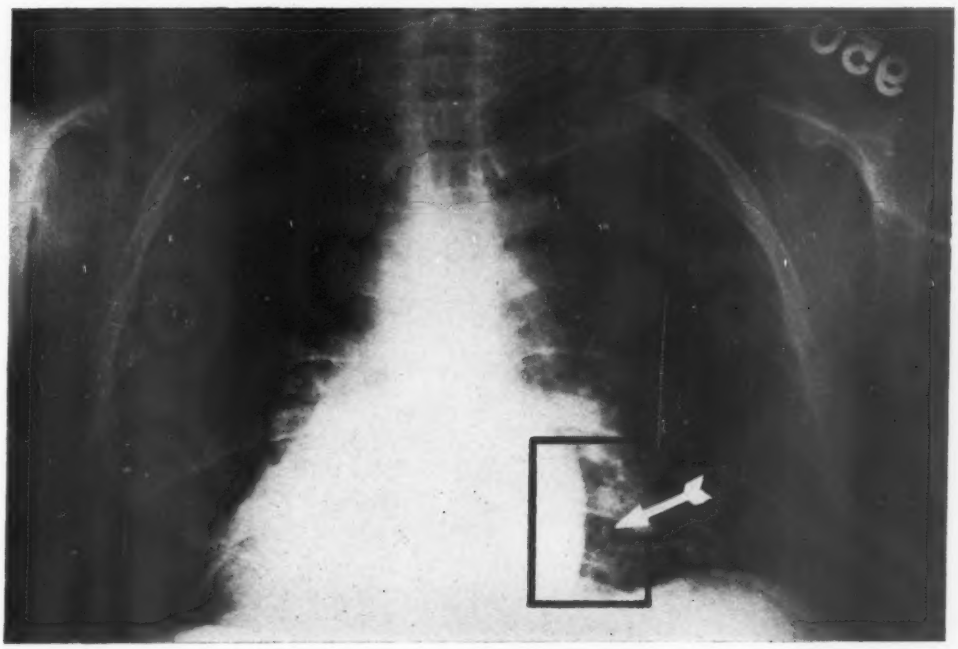

Fig. 1.—Arrow indicates needle in pericardium.

Fig. 1A.—Enlargement of section showing needle fragments.

On July 22, 1942, the patient entered the Mt. Sinai Hospital, New York City, Surgical Service of Dr. Harold Neuhof.* On July 23, 1942, abdominal paracentesis was done and 8,000 c.c. of straw-colored fluid were removed. The blood pressure was 105/80.

*I am indebted to Dr. Neuhof for permission to summarize the patient's subsequent course.

Operation by Dr. Harold Neuhof: Under nitrous oxide, oxygen, and ether, oro-endotracheal anesthesia, an incision was made in the right third intercostal space, in a transpleural approach. Evidence of an old inflammatory process was noted in the intercostal muscles. The right side of the heart was exposed, and the amplitude of the cardiac excursions was seen to be distinctly diminished. A large pericardio-diaphragmatic adhesion was seen and divided. The pericardium was thick, indurated, and densely adherent. The epicardium and pericar-

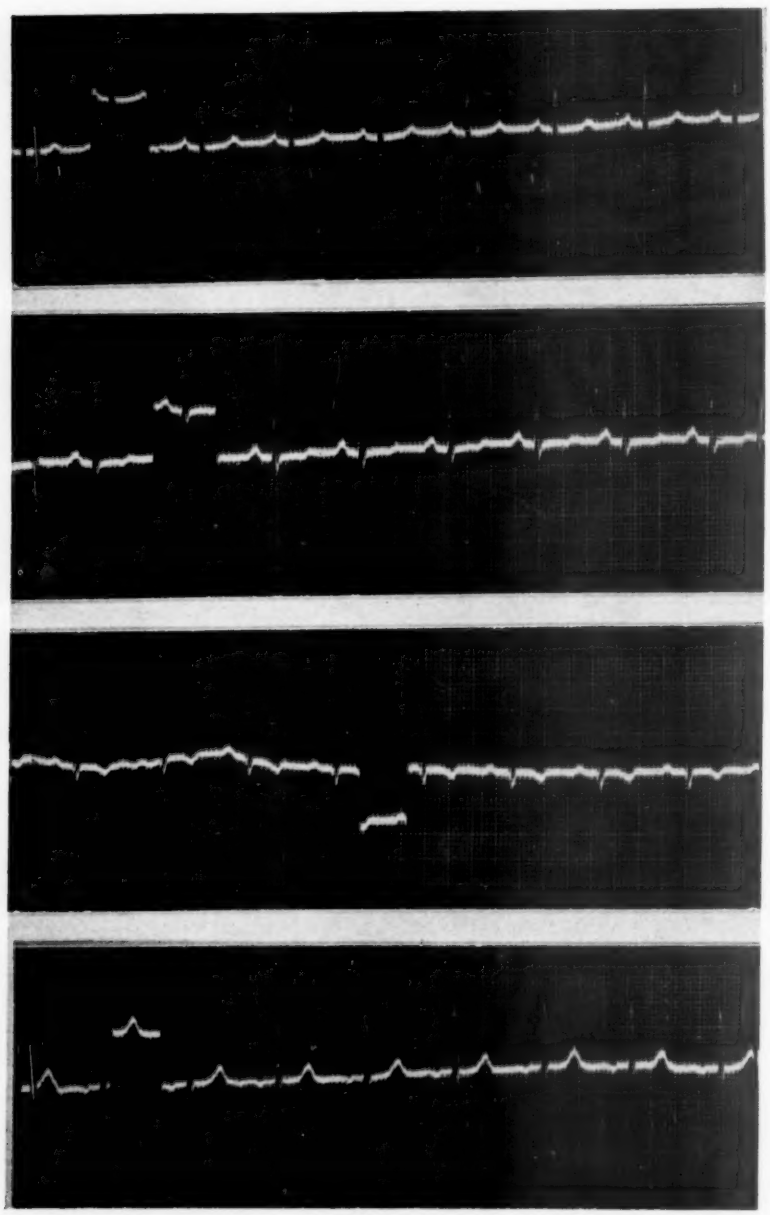

Fig. 2.

dium were completely fused over the exposed portion of the heart. The pericardium over the right side of the heart was dissected away and removed. In the region of the inferior vena cava, the needle was found in two pieces in a dense, fibrous sheath, and removed. No attempt was made to free the left side of the heart. Sulfathiazole was placed in the operative field. Closed drainage was instituted in the right axilla and the chest wound was closed.

The patient left the operating room in excellent condition. His blood pressure at onset of the operation was 104/64. When the pericardium was opened, the blood pressure rose from 84/45 to 128/80. This rise in blood pressure was maintained throughout the postoperative period, indicating that the heart had been effectively freed. The day after the operation the patient developed a purulent bronchitis which rapidly progressed to bronchopneumonia. Despite the administration of oxygen, several bronchoscopic procedures, sulfadiazine, and supportive measures, the patient died on the third postoperative day, July 26, 1942. Death apparently was caused by suppurative bronchopneumonia.

The pathologist reported fragments of thickened pericardium, showing marked fibrosis, with hyalinization and focal lymphocytic infiltration. The second fragment of pericardium showed the foreign body (needle).

An autopsy was not obtained.

SUMMARY AND CONCLUSIONS

A case is presented in which chronic constrictive pericarditis developed six years after the accidental deposition of a portion of a surgical needle in the pericardium.

White[6] observes that trauma resulting in hemopericardium may leave chronic adhesive pericarditis. This is due to fibrosis following organization of the blood. In this case the pathogenesis is probably related to two factors:

1. The development of an acute inflammatory process, beginning at the site of the needle. This is substantiated by evidence of an old infection of the intercostal muscles along the course of the needle, and by the development of a pericardial effusion about two weeks after the injury.

2. Fibrosis due to chronic irritation of the pericardium because of the needle itself. This idea is supported by the fact that the thickening, fibrosis, and induration of the pericardium were maximal at the locus of the needle.

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REPORT OF A CASE OF PAROXYSMAL VENTRICULAR TACHYCARDIA, WITH NO DEMONSTRABLE ORGANIC HEART DISEASE, WHICH PRODUCED ATTACKS OF SYNCOPE

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PAROXYSMAL ventricular tachycardia is a condition that is not often encountered. Although it has been reported for many years, writers usually point out the fact that it is a rare condition. It is not common in association with organic heart disease; much less commonly is it found in cases in which no organic cardiac lesion is evident. In a recent review[1] of thirty-six cases from the records of the Heart Station of the Boston City Hospital, the incidence was one in every 1,800 electrocardiograms. Of the thirty-six cases, there was only one in which ventricular tachycardia occurred without heart disease (1 in 64,800 tracings).

By far the greatest number of cases in which ventricular tachycardia occurs are cases of arteriosclerotic heart disease, often associated with hypertension. It occurs after coronary thrombosis and in rheumatic heart disease. It would therefore be expected that the largest incidence would be found among older patients. However, it may occur at any age. Amberg and Willius[2] reported its occurrence in a female infant of 15 months who had cardiac hypertrophy of unknown origin. Wolferth and McMillan[3] reported four cases of paroxysmal ventricular tachycardia, and the ages of two of the patients were 18 and 20 years, respectively. In both cases there was evidence of organic cardiac disease.

CASE REPORT

C. J. H., a soldier, 27 years of age, was admitted to the Camp Myles Standish Station Hospital Jan. 9, 1943, complaining of attacks of dizziness, palpitation, and occasional syncope. Physical examination disclosed a medium-sized man who was worried over these distressing attacks which had been coming on since October, 1942. Heart examination disclosed occasional premature systoles. There was no enlargement, the heart sounds were of good quality, and no murmurs were heard. The blood pressure was 112/70.

Past History.—Diphtheria at the age of 5 years; scarlet fever at the age of 6 years; chicken pox at the age of 8 years. There was no history of rheumatic fever. He had never had attacks prior to October, 1942. In civil life he had been a cigar salesman.

Family History.—His father had had pulmonary tuberculosis, but is now considered cured. His mother and eight brothers are living and well.

The patient said that his first attack occurred early in October, 1942. He felt sudden dizziness, fullness of the neck, and a sense of weakness.

Received for publication June 13, 1943.

He continued to have attacks of this nature, and occasionally he lost consciousness. He always recovered rather promptly without ill effects, and was able to resume his duties where he had left off. The most severe attack occurred Nov. 7, 1942, while he was working at a mimeograph machine. He lost consciousness for several minutes (3 to 5 minutes, according to witnesses). When he recovered, he was able to continue to operate the machine and to finish the task to which he had been assigned. This attack prompted him to report to the dispensary, where he was observed, and later sent to a hospital. No diagnosis was made. After his discharge, he continued to have attacks and was admitted to the Station Hospital.

An electrocardiogram taken Jan. 23, 1943, showed rather frequent premature ventricular systoles, occasionally in couples (Fig. 1). The patient was observed for many days, but during his stay in the hospital he did not have any attacks. No diagnosis was made, except cardiac arrythmia due to premature ventricular systoles.

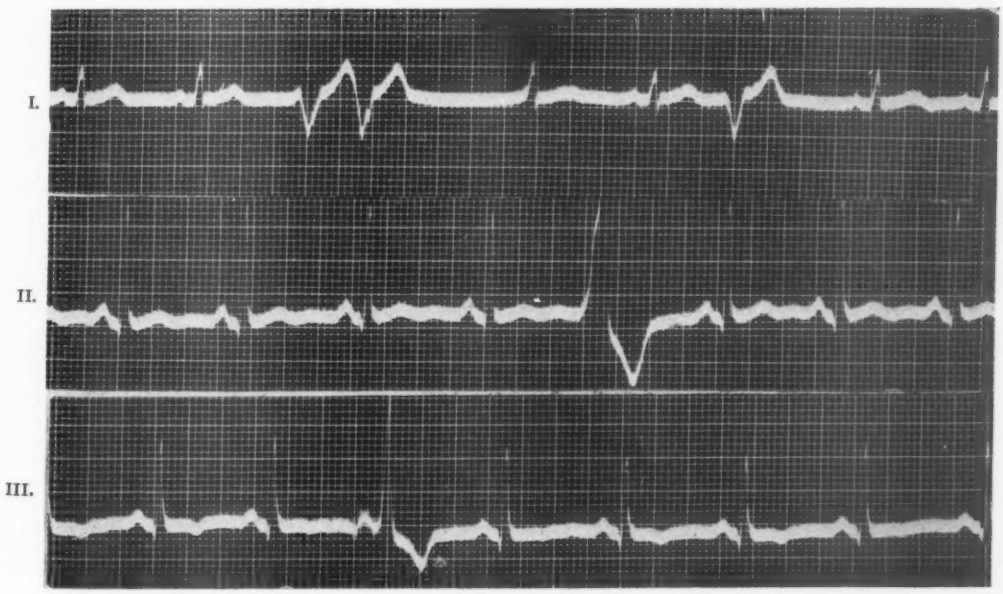

Fig. 1.—C. J. H., Jan. 23, 1943. Shows premature ventricular systoles. Note the two successive ones in Lead I.

He was told to report any further attacks, and, on Feb. 16, 1943, he returned to the hospital. He complained again of successive attacks of dizziness, fullness in the neck, and fainting. He did not complain of precordial pain or respiratory distress. It should be noted that while he complained of palpitation occasionally, this was never a major subjective symptom.

Examination at this time again disclosed the frequent premature systoles, but, more than that, runs of tachycardia were also noted. A long tracing of Lead II was taken. Fig. 2 shows a characteristic portion of that tracing. The upper strip shows the premature ventricular systoles. The lower strip shows unidirectional paroxysmal ventricular tachycardia, lasting 5.2 seconds. Characteristically, the attacks began abruptly and ended abruptly, giving place to sinus

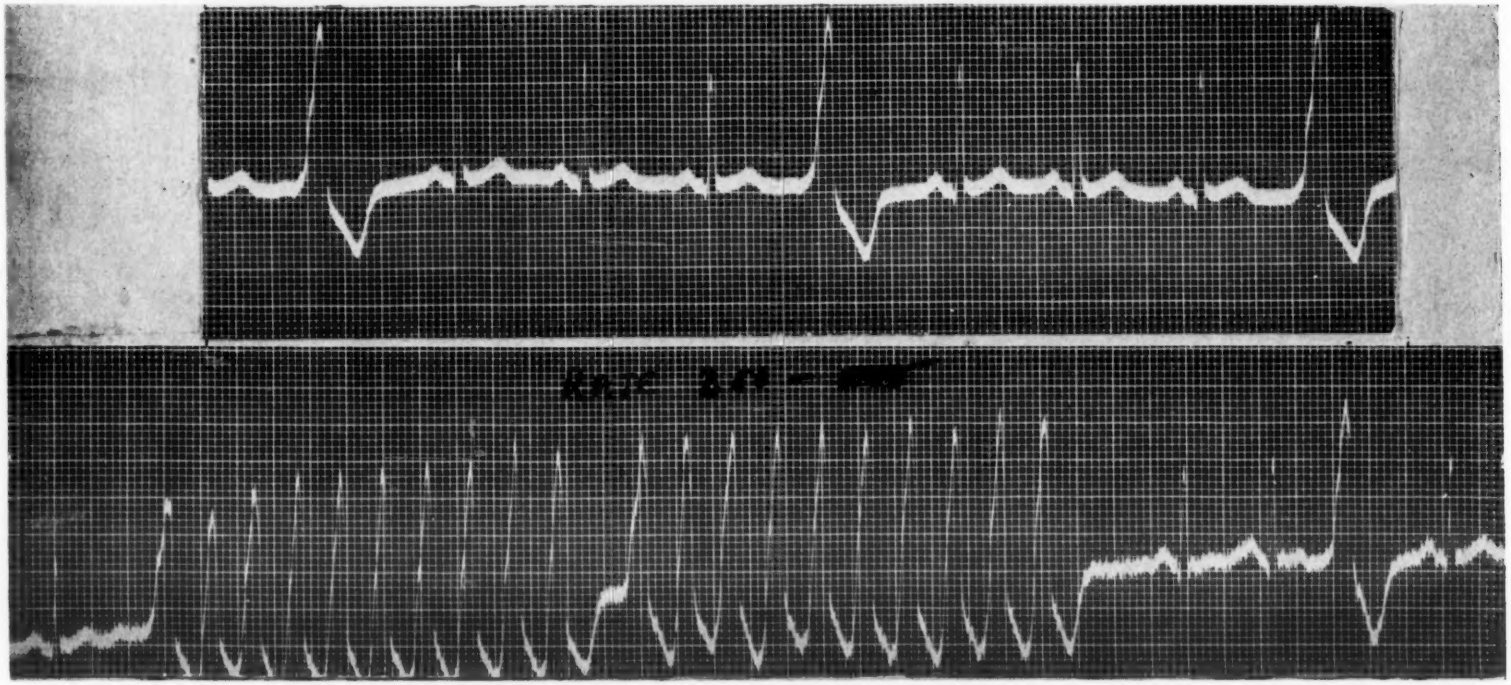

Fig. 2.—C. J. H., Feb. 16, 1943. Lead II shows a run of paroxysmal ven ricular tachycardia lasting 5.2 seconds. The upper strip is part of the same lead taken at the same sitting.

rhythm with occasional premature ventricular systoles. Many attacks were recorded on this long tracing; the longest is reproduced here.

On March 12, 1943, another tracing showing attacks of paroxysmal ventricular tachycardia was obtained. In this tracing, the attacks were recorded in the three limb leads and in CF_4 (Fig. 3). If the ectopic ventricular beats in this tracing are compared with those of Fig. 1, it will be noted that there is a close resemblance between the complexes of the tachycardia and the premature ventricular systoles.

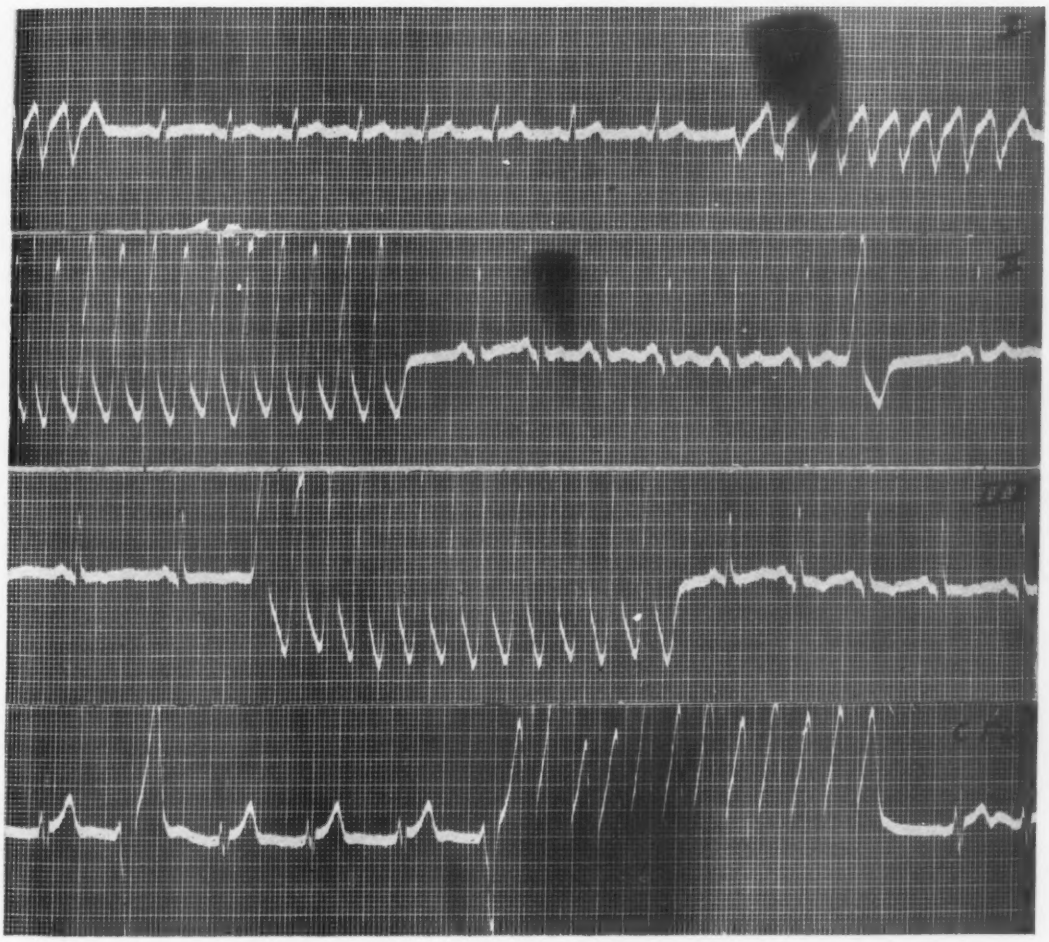

Fig. 3.—C. J. H., March 15, 1943. Runs of paroxysmal ventricular tachycardia in the three limb leads and CF_4. Note resemblance of ventricular complexes to those in Fig. 1, especially in Lead I.

It is believed, therefore, that the focus of origin of the attacks of tachycardia was the same as that which gave rise to isolated premature systoles.

During the recording on March 15 the patient did not faint, but was frequently on the verge of losing consciousness. Evidently no attack was long enough to seriously impair cerebral circulation. Furthermore, the patient was lying flat on the examining table.

Laboratory Data.—Urine: normal except for occasional leucocytes. Erythrocyte count: 4,777,000; hemoglobin, 90 per cent. Nonprotein nitrogen, 39 mg. per cent; sugar, 82 mg. per cent. Basal metabolic rate: (a) +20 per cent, (b) −3 per cent. Chest roentgenogram: "The heart is of moderate size; there is no apparent enlargement, and the general contour as seen in the A-P view appears normal. The arch of the aorta is within normal limits." The pulmonic area was normal.

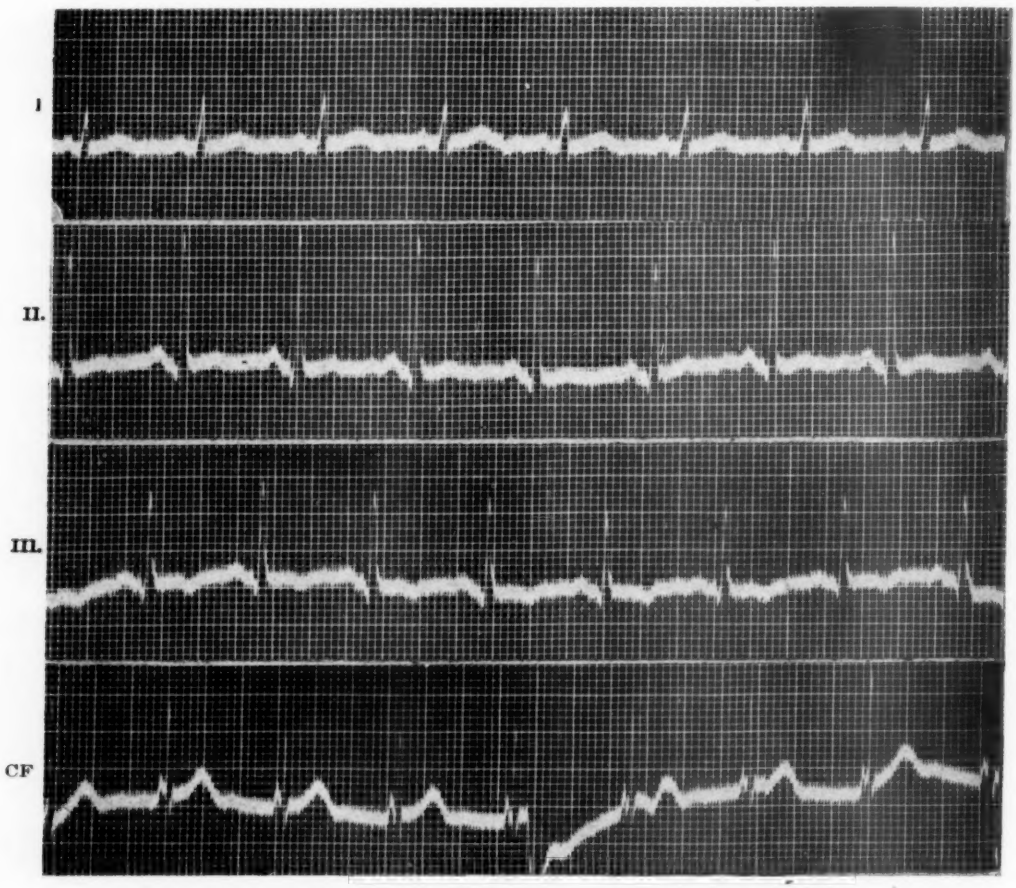

Fig. 4.—C. J. H., May 4, 1943. Shows effect of quinidine sulfate therapy. Note the absence of premature ventricular systoles and the effect of the drug on the T waves.

On March 19, 1943, quinidine sulfate therapy was started. The patient was given the drug first in test doses, and then in larger doses. On March 22 the dose was 18 grains a day, and this was established as an adequate maintenance dose. Daily examinations for weeks during quinidine therapy have shown occasional premature ventricular systoles which seem to have become rarer with the passage of time. On March 25 a tracing showed only one premature ventricular systole. Tracings were taken frequently to note the effects of the quinidine, and, after a reduction of the dose to 15 grains a day, a tracing taken April 3, 1943, showed more frequent premature ventricular systoles,

and, in Leads III and CF_4, there were two consecutive premature ventricular systoles. The dosage was raised to 18 grains again. Since then, the patient has had no attacks of paroxysmal ventricular tachycardia and no syncope. Fig. 4 shows a tracing taken May 4, 1943, after forty days of quinidine therapy. Note that there are no ectopic systoles; the effect of quinidine on the T waves is apparent. The patient has had no symptoms of quinidine toxicity.

SUMMARY

1. A case of paroxysmal ventricular tachycardia is described; this occurred in a male soldier, aged 27 years, who had no organic heart disease.

2. Electrocardiograms are presented showing (a) premature ventricular systoles, (b) attacks of paroxysmal ventricular tachycardia which stemmed from the same source as the premature ventricular systoles, and (c) the effects of quinidine sulfate.

3. The efficacy of quinidine sulfate in the prevention of paroxysmal ventricular tachycardia is demonstrated.

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MASSIVE CARDIAC HYPERTROPHY

A Case Report

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IT IS not uncommon to find large hearts at the autopsy table, but weights in excess of 1,000 grams are rare, if one may judge by the number of case reports. In the past one hundred years, less than fifty cases have been reported in which the heart weighed more than 1,000 grams. In the majority of instances, such enlarged hearts were found to be the seat of valvular deformities, either single or multiple, of adhesive pericarditis, or of some sort of congenital defect.[1] In addition, there were usually other abnormalities, such as high blood pressure, chronic pulmonary disease, hyperthyroidism, chronic nephritis, deformities of the thorax, peripheral arteriovenous fistulae, von Gierke's disease, myxedema, beriberi, myocardial infarction, and interstitial myocarditis (Fiedler's myocarditis).[2-4] In approximately 15 per cent of these cases, however, the cause of the massive hypertrophy was not discovered. These cases have been classed by some pathologists under the heading of idiopathic cardiac hypertrophy. We desire to present a case of cardiac hypertrophy which was discovered clinically and confirmed at autopsy in a patient who had had previous myocardial infarction without actual coronary occlusion.

CASE REPORT

A 66-year-old white physician walked into the Jewish Hospital Nov. 22, 1942, stating that, while engaged in his usual professional rounds, he was seized with severe precordial pain which radiated to the left shoulder and down the left arm. He had marked shortness of breath. Three weeks earlier he had a similar attack while attending a wrestling match. At that time he was hospitalized for one day and was discharged symptom free. An electrocardiogram then showed no evidence of recent cardiac damage. The past medical history was irrelevant except that for the preceding year he had had numerous sore throats and had taken small doses of sulfonamides frequently. He was a sthenic person who had been active athletically all of his life.

Physical examination disclosed a man who appeared extremely ill. His color was ashen. His skin was cold and clammy. The respirations were 40 per minute. The rectal temperature was 97° F. The blood pressure was 152/92 in the right arm and 142/90 in the left arm. His pulse was weak and thready, and its rate was 150 per minute. The heart sounds were distant. There was a protodiastolic gallop at the base, and occasional extrasystoles were heard. The left border of the heart extended to the anterior axillary line. The lungs were normal.

From the Medical Service of the Jewish Hospital, Philadelphia, Pa.
Received for publication July 5, 1943.

The edge of the liver was palpable 4 cm. below the right costal margin. There was evidence of peripheral arteriosclerosis, but no edema.

Emergency treatment consisted of morphine sulfate (⅙ grain), atropine sulfate (1/150 grain), papaverine hydrochloride (1 grain), and the use of an oxygen tent. The patient had a leucocytosis of 13,000, with a polymorphonuclear count of 90 per cent. The erythrocyte sedimentation rate was 18 mm. in one hour (our normal, 9 mm.). An electrocardiogram at this time showed a relatively rapid tachycardia, with left bundle branch block. During the first few days the patient's condition remained critical. Gallop rhythm persisted. Dyspnea and cyanosis were marked. The blood pressure fell to 110/70, and moisture appeared at the bases of both lungs. The patient was slowly digitalized, and soon appeared and felt much improved. Convalescence was uneventful until the evening of Dec. 11, 1942, when he developed, while speaking to his relatives, sudden, flaccid, right-sided hemiplegia, with aphasia. The intravenous administration of a grain of papaverine resulted in the return of speech in two or three minutes, and he was soon able to move his right arm and leg. By the next day, no residual signs remained. On Dec. 20, 1942, the patient enjoyed a hearty breakfast and sat up in bed to read a newspaper. Twenty minutes later he was found dead.

Autopsy was performed two hours after death. The heart weighed 1,150 grams. The left ventricular wall varied from 21 to 26 mm., and the right ventricular wall, from 5 to 6 mm., in thickness. Moderate coronary atherosclerosis was present, but the lumina of the vessels were very wide; the coronaries measured as much as 1 cm. in circumference. There was no evidence of occlusion. On the lateral aspect of the left ventricle an area of necrosis and mucoid degeneration, with hemorrhage, approximately 3 cm. in diameter, was seen. The cardiac musculature showed moderate fibrosis, especially near the apex. The papillary muscles were markedly hypertrophied and fibrotic.

Microscopic sections of the heart muscle showed hypertrophy of all fibers. The amount of fibrous interstitial tissue was increased, and active fibroblastic proliferation was present. There was no evidence of perivascular inflammation. Sections of the area of myocardial necrosis revealed degeneration and necrosis of muscle fibers, invasion by fibroblasts, and early collagen deposition and lymphocytic infiltration.

COMMENT

A case of massive cardiac hypertrophy is presented, in which there were no valvular lesions or other possible causes for the enlargement. In considering the diagnostic possibilities, for the sake of completeness, at least, one should not forget myocarditis of unknown origin, as described by Fiedler,[2-4] which occurs with no other demonstrable disease that can be correlated with the cardiac state. The appearance of this type of interstitial myocarditis in apparently healthy persons who more or less suddenly develop progressive myocardial failure has been described by a number of other investigators. Such patients are prone to suddenly develop dyspnea, cyanosis, tachycardia, weakness, and to die suddenly, as was the case with our patient. In most of the cases reported, however, the patients were between the ages of 20 and 50 years. Microscopic examination of these hearts shows diffuse infiltra-

tion of interstitial tissue by lymphocytes, monocytes, and, to a lesser degree, polymorphonuclear, eosinophile, and plasma cells. Numerous fibroblasts and new blood vessels are also observed. The pathologic and histologic picture in our case was not that of myocarditis. The athletic history of the patient may have had some bearing. The case is of unusual interest, not only because of the size of the heart, but because of the absence of explanatory pathologic changes within the heart itself or elsewhere.

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Abstracts and Reviews

Selected Abstracts

Lange, K., and Linn, J. B.: Use of Fluorescein Method in Establishment of Diagnosis and Prognosis of Peripheral Vascular Diseases. Arch. Int. Med. 74: 175, 1944.

Fluorescein, when injected intravenously, can be made visible by a beam of long wave ultraviolet radiation on reaching any area of exposed skin or mucous membranes with the blood stream.

The physical prerequisites for a good visualization of fluorescein in the tissue and capillaries are the use of an appropriate long wave ultraviolet ray source and a darkroom. A photoelectric method to indicate the arrival of the dye and to measure the intensity of staining may also be used.

Fluorescein is not toxic. Over 1,000 patients have been examined by this method without untoward reactions, except that 11 patients had vomiting of short duration during the injection. Experiments on animals showed extremely low toxicity. The dye travels with the blood stream and diffuses immediately through the capillaries into the interstitial spaces. Dead cells do not stain. Fluorescein is partly adsorbed to the plasma proteins. Pathologic changes in plasma proteins do not change the amount of fluorescein immediately available for diffusion.

Ultrafiltration experiments show that the amount of dye diffusing into the tissue depends on intracapillary pressure; if the latter rises, the amount which diffuses into the tissue with the water increases without changing the concentration. Changes in capillary permeability change the amount which diffuses as well as the concentration. Even slight inflammation increases the fluorescence of the tissue. Pigmentation, especially in colored people, makes the test unreliable, although certain basic facts can still be elicited. The degree of fluorescence depends on the amount of blood flowing through a certain part of the body. Objective determinations of circulation time in normal persons showed that the circulation time between the arm and the lips is between fifteen and seventeen and one-half seconds, while the time to the legs normally should not exceed twice this figure.

Nine patients with acute embolism of the legs were examined. It was possible to define exactly the lowest possible level of amputation as far as the skin is concerned and to decide immediately on the probable formation of sufficient collateral circulation to avoid amputation.

Block of the sympathetic lumbar ganglions should be performed to avoid mistakes caused by vasospasm.

The immediate diagnosis of thrombotic occlusion can also be made.

Small gangrenous areas in arteriosclerotic peripheral vascular disease can be judged as to the prospect for healing, localization, or further spread.

There are two functional types of arteriosclerotic peripheral vascular disease as shown by this test. The first form concerns the larger vessels, mainly causing rapidly spreading gangrene in the periphery, while the other occludes mainly small arteries with capillaries, thereby not necessitating large amputations.

Thromboangiitis obliterans has usually a higher fluorescence than one would expect from the lack of arterial pulsations. This discrepancy is a leading sign. Spotty fluorescence may complete the picture.

Vasospastic disorders have a low fluorescence during the attack, which immediately returns to normal or even increases above normal on blockage of the sympathetic chain.

Rubor on an inflammatory basis in a limb with arteriosclerotic peripheral vascular disease can be well differentiated from venous congestion (rubor on dependency).

Thrombophlebitis of superficial vessels can be well made out as long as it is inflammatory and the extent of the inflammation can be outlined.

Ulcers of the leg on a varicose vein basis can be judged as to their outlook for healing and skin grafting. Syphilitic ulcers of the leg have a specific picture in the fluorescein test which distinguishes them from varicose vein ulcers.

AUTHORS.

Bain, C. W. C.: Incomplete Bundle Branch Block. Brit. Heart J. 6: 139, 1944.

Six cases of incomplete bundle branch block have been described. In none did the duration of the QRS exceed 0.10 second when incomplete bundle branch block was judged to be present. In all of the cases normal complexes have been present for comparison, either in the same record or within a short period.

The evidence suggests that the cases could be divided into three groups.

The first shows a slight increase in the QRS without axis deviation as exemplified by the aberrant ventricular response to an auricular premature systole. These are probably due to a bilateral delay down each main branch (Case 1).

The second shows delay down one branch, fulfilling the criteria for bundle branch block except that the QRS does not exceed 0.10 sec. (Cases 1, 2, 3, 4 and 6).

The third shows transitional complexes (Cases 5 and 6). In these cases it is likely that the transitional complexes were due to a combination of bilateral delay down each main branch with additional delay down one branch, since both cases had an unstable branch block which sometimes changed from right to left, and there was not much axis deviation, although the QRS duration was 0.10 second.

AUTHOR.

Hume, W. E., and Szekely, P.: Cardiac Involvement in Spirochaetal Jaundice. Brit. Heart J. 6: 135, 1944.

The authors report a case of spirochetal jaundice with electrocardiographic evidence of transient myocardial involvement. For five days following admission the electrocardiogram showed auricular fibrillation and a sinus rhythm with T-wave changes, all of which had disappeared four months later. It is believed that, if more extensive studies were made in cases of jaundice, especially those with very low blood pressure and changes in the character of the heart sounds, more instances of myocardial involvement might perhaps be encountered.

The authors believe that the electrocardiographic changes can be accounted for by direct involvement of the heart either in the form of multiple hemorrhages or of toxic damage to the heart muscle, or both.

AUTHORS.

Bramwell, C., and Jones, A. M.: Acute Left Auricular Failure. Brit. Heart J. 6: 129, 1944.

Two cases of mitral stenosis with acute pulmonary edema leading to death about the middle stage of pregnancy are described.

The mechanism of production of this complication is discussed and it is attributed to acute left auricular failure.

AUTHORS.

Rich, A. R., and Gregory, J. E.: Further Experimental Cardiac Lesions of the Rheumatic Type Produced by Anaphylactic Hypersensitivity. Bull. Johns Hopkins Hosp. **75**: 115, 1944.

In preceding papers we have described and illustrated cardiac lesions of the rheumatic type that were produced in animals by hypersensitive reactions to foreign protein; shown the basic identity of rheumatic pneumonitis with the pneumonitis resulting from sulfonamide hypersensitivity in nonrheumatics; and assembled evidence of a variety of other types in support of the view that human rheumatic lesions represent the results of focal hypersensitive reactions. In the present paper further experimental cardiac hypersensitive lesions of the rheumatic type are illustrated. Studies illustrating experimental hypersensitive pneumonitis and arthritis will be presented shortly.

AUTHORS.

Wilson, M. G., and Lubschez, R.: Recurrence Rates in Rheumatic Fever: The Evaluation of Etiologic Concepts and Consequent Preventive Therapy. J. A. M. A. **126**: 477, 1944.

The expected risk for a major recurrence of rheumatic fever at specific ages from 4 to 25 years and for various patterns of disease was defined from the analysis of the records of 499 rheumatic individuals during 5,677 person-years of life experience.

The only factors which were found to influence the risk of future recurrences were age and the interval of time elapsing since the last attack.

Most published studies on the relative frequency of rheumatic fever in experimental and control groups do not appear to meet the basic requirements for adequate biostatistical analysis. Final judgment as to the validity of etiological concepts and consequent preventive therapy, which are based on these studies, must be deferred.

AUTHORS.

Jones, T. D.: The Diagnosis of Rheumatic Fever. J. A. M. A. **126**: 481, 1944.

For the present, it would seem advisable to limit the diagnosis of rheumatic fever to patients with rather distinct clinical manifestations. It is suggested that the following constitute reasonably certain diagnostic criteria:

Any combination of the major manifestations (carditis, arthralgia, chorea, nodules, and a verified history of previous rheumatic fever).

The combination of at least one of the major manifestations with two of the minor manifestations (fever, abdominal or precordial pain, erythema, marginatum, epistaxis, pulmonary changes, and laboratory abnormalities).

The presence of rheumatic heart disease increases the diagnostic significance of the minor manifestations when no other cause for these manifestations exists.

Small though probably insignificant errors may be found with these criteria. Numerous clinical entities as enumerated may be confused with rheumatic fever. Clinical observations and, wherever possible, specific diagnostic tests should be applied in any diagnostic problem.

AUTHOR.

Van Ravenswaay, Arie C.: The Geographic Distribution of Hemolytic Streptococci: Relationship to the Incidence of Rheumatic Fever. J. A. M. A. **126**: 486, 1944.

Bacteriologic studies at eight Army Air Forces installations during the period from Jan. 1 to April 21, 1944, reveal that Group A hemolytic streptococci isolated

from cases of upper respiratory disease, scarlet fever, and acute rheumatic fever belonged to a multiplicity of Lancefield types.

At none of the posts studied was a single epidemic strain responsible for the streptococcic disease observed.

At the posts studied, bacteriologic data obtained after the development of acute rheumatic fever were not applicable to the preceding upper respiratory infections.

An apparent correlation was observed between post survey (carrier) rates from Group A hemolytic streptococci, incidence rates for scarlet fever, and the incidence of acute rheumatic fever.

AUTHOR.

Thomas, C. D.: Prevention of Recurrences in Rheumatic Subjects. J. A. M. A. **126:** 490, 1944.

The belief is expressed that, in spite of the difficulties involved, the increasingly widespread use of prophylactic sulfonamides will bring tremendous advance in the problems of rheumatic fever and rheumatic heart disease.

AUTHOR.

Rutstein, D. D.: The Role of the Cardiac Clinic in the Rheumatic Program. J. A. M. A. **126:** 484, 1944.

A community rheumatic fever program is essential if complete care is to be given to patients suffering from rheumatic disease, and the cardiac clinic with an affiliated registry should serve as the focus around which the community rheumatic fever program should be built.

AUTHOR.

Wellen, I., Welsh, C. A., and Taylor, H. C.: The Effect of Pregnancy and Renal Function in Women With Pre-Existing Essential Hypertension and With Chronic Diffuse Glomerulonephritis. J. Clin. Investigation **23:** 742, 1944.

Renal function studies made upon patients with essential hypertension indicate that pregnancy is associated with a slight temporary increase in renal blood flow. Glomerular filtration rate and the tubular excretory mass (Diodrast Tm) are unaffected by pregnancy in these women.

Comparison of results obtained during pregnancy and for an observation period of one to four years after delivery indicate that pregnancy itself, when uncomplicated by specific toxemia, does not cause any deterioration of renal function in women with essential hypertension or chronic glomerulonephritis.

AUTHORS.

Rappaport, M. B., and Luisada, A. A.: Indirect Sphygmomanometry. A Physical and Physiologic Analysis and a New Procedure for the Estimation of Blood Pressure. J. Lab. & Clin. Med. **29:** 638, 1944.

An apparatus is described which can register graphically and simultaneously all of the physiologic phenomena which must be evaluated for the estimation of blood pressure by the palpatory, oscillatory, and the auscultatory methods. This graphic device eliminates the human element with its subjective differences in the appreciation of the physiologic signs and makes possible a quantitative comparison of the associated phenomena.

The theoretical principles fundamental to the palpatory, oscillatory, and the auscultatory methods are discussed. With the aid of the above mentioned apparatus, the authors have observed:

1. In an oscillometric curve, the configuration of the pulse wave is modified between the limits of systolic and diastolic pressure. The degree of modification

is a function of the systolic, diastolic, and cuff pressures. The wave form is unmodified only when the cuff pressure is lower than the diastolic pressure level.

2. Diastolic pressure is represented in the oscillometric curve by the first arterial pulsation which is undistorted during its most negative phase.

3. The oscillatory method is reliable in the estimation of the systolic blood pressure only when accurate sphygmographic registrations are made. Inaccurate or poor sphygmograms do not indicate distinctly the initial appearance of the minute wave which represents the beginning of ejection of blood into the artery as differentiated from the surpramaximal oscillations.

4. The gradual tapering-off of the pulse amplitude in an oscillometric curve below the diastolic pressure level commonly described is not a physiologic phenomenon but a definite instrumental error. This is essentially due to a diminution in the efficiency of the cuff as a detector of arterial pulsations when the pressure is lowered. The use of independent pressure and registration cuffs eliminates this source of error.

5. The Korotkow sounds occur simultaneously with the sharp primary oscillation of the brachial pulse which is the beginning of the ejection of blood into the artery.

6. There are two major contributing factors to the production of the Korotkow sounds; the mechanism of each is described.

7. The first distinct Korotkow sound (systolic pressure level) generally occurs simultaneously with the first distinct sharp primary oscillation of an oscillometric curve. The first suddenly diminished Korotkow sound (auscultatory diastolic pressure level) corresponds very closely to the first undistorted arterial pulsation.

8. An explanation is given for the sudden diminution in the intensity of the Korotkow sounds at diastolic pressure.

9. As a general rule, the systolic pressure is underestimated because the first Korotkow sound which appears during a gradual cuff deflation possesses an intensity below human audibility.

10. Diastolic blood pressure as judged by the auscultatory method (when the sounds suddenly become dull and muffled) corresponds exactly with the recorded values and within close limits with the negative transition effect of the oscillometric curve. Any other sound phase does not bear any relationship whatsoever with diastolic pressure.

11. The stethoscopic method of sound registration shows the first Korotkow sounds (systolic pressure level) most distinctly, whereas the logarithmic method registers the sudden diminution (diastolic pressure level) more distinctly than the stethoscopic method.

12. In some instances, the sudden muffling effect at the diastolic pressure level is not audible. In such cases, the graphic method may show this diminution effect with sufficient clarity to accurately estimate the diastolic blood pressure.

13. Considerable error may be introduced when estimating the systolic blood pressure by the palpatory method. The degree of error may be in the order of several millimeters of mercury below the actual value.

14. The diastolic pressure level cannot be estimated by the palpatory method, because the sense of human feeling cannot detect the instant when the arterial pulsation initially attains an undistorted configuration.

The graphic registration method which registers all of the physiologic phenomena associated with indirect sphygmomanometry, has application in the more exact studies of blood pressure. The method shall prove useful in the clarification of such phenomena as the auscultatory gap, the double tone of Traube, the double murmur of Duroziez, the murmur accompanying the pistol shot pulse, etc.

AUTHORS.

de Takats, G.: The Value of Sympathectomy in the Treatment of Buerger's Disease. Surg., Gynec. & Obst. **79**: 359, 1944.

Sympathectomy deprives the extremity of its vasoconstrictor tone. It does not influence the course of Buerger's disease. However, when this disease is in an inactive phase and when adequate preoperative tests reveal the presence of sufficient collateral vascular supply, sympathectomy will aid an extremity considerably whose vessels have been crippled by recurrent attacks of segmental thrombosis. In this series of 50 patients 136 sympathectomies have been done; about one-half of those patients have also had minor amputations combined with sympathectomy. Of the 50 patients, 37 have been rehabilitated to full-time work, 7 are doing part-time work, and only 6 are invalids. In addition to foot hygiene and complete abstinence from tobacco, a change of occupation is important for those whose feet are continuously subjected to an exposure to cold or trauma.

AUTHOR.

Benians, T. H. C.: A Vasospastic Factor in the Serum of a Case of Raynaud's Disease With Cold Agglutination Experiments on Rabbits. J. Lab. & Clin. Med. **29**: 1074, 1944.

A serum containing high titer cold antibodies, and derived from a case of Raynaud's disease, is shown to cause fatal pulmonary artery spasm in rabbits when given, cold, intravenously. This effect is mitigated by giving the serum warm. It is suggested that these cold antibodies have a direct effect, probably of an allergic type, on arterial musculature both in the experimental animal and the clinical case. It is further suggested that the frequent association of cold antibodies with a Wassermann-like body point to an origin of the former from diseased vascular structures and this again would help to explain their action on both blood cells and vessels. A possible function of cold antibodies in normal vascular control is mentioned, these may or may not be the basis of prototype of the high titer cold antibodies.

Preliminary experiments in protection against the cold antibodies by the intravenous injection of lipoids have been carried out with some success.

AUTHOR.

Taylor, C.: Some Properties of Maximal and Submaximal Exercise With Reference to Physiological Variation and the Measurement of Exercise Tolerance. Am. J. Physiol. **142**: 200, 1944.

Thirty-one subjects have been given a test twice, consisting of a four-minute walk on the treadmill and a run to exhaustion after a four-minute, interim rest, the retest following in three days. Heart and respiration rates, ventilation, blood lactate, per cent of oxygen and CO_2, and oxygen consumption were determined during the walk and during the last minute of the run, and the first three of these measures throughout both walk and run. From these data it has been possible to evaluate the sources of variation in the physiologic measures and their validity as indicators of fitness.

AUTHOR.

Fine, J., and Seligman, A. M.: Traumatic Shock. VII. A Study of the Problem of the "Lost Plasma" in Hemorrhagic Tourniquet, and Burn Shock by the Use of Radioactive Iodo-Plasma Protein. J. Clin. Investigation **23**: 720, 1944.

Plasma proteins tagged with radioactive iodine were used to study the capillary leakage hypothesis in hemorrhagic, tourniquet, and burn shock. No evidence of leakage due to a change in the permeability of the generalized capillary bed was

found. Tagged plasma proteins escaped into areas of injury in considerable amounts, but not into untraumatized areas. This was also true after plasma infusion.

There is also evidence to show that the general capillary bed does not become more permeable to plasma proteins or plasma in the late or irreversible phase of hemorrhagic shock following transfusion.

Following saline therapy in hemorrhagic shock, plasma proteins are carried out of the blood stream with saline. This occurs to a greater extent in irreversible than reversible hemorrhagic shock. The volume of dilute plasma lost in this way is small.

AUTHORS.

Fine, J., Frank, H. A., and Seligman, A. M.: Traumatic Shock. VIII. Studies in The Therapy and Hemodynamics of Tourniquet Shock. J. Clin. Investigation 23: 731, 1944.

The application of tourniquets to both hind legs of unanestheized dogs for five hours is not always followed by shock. If shock occurs, it is of moderate intensity. Saline solution given intravenously is curative.

The application of tourniquets to unanesthetized dogs for eight to eleven hours will uniformly produce shock which is fatal if untreated. Intravenously administered plasma, 5 per cent bovine albumin in saline solution, or 25 per cent bovine albumin supplemented by peroral fluid are effective therapeutic agents, if the deficiency in plasma volume is made good while the blood pressure is above 60 mm. Hg. Occasionally, they may be effective at blood pressures between 60 and 40 mm. Hg. Physiologic saline, 25 per cent albumin without peroral fluid, and 5 per cent saline with peroral water are not effective.

The critical blood pressure level of tourniquet shock is much higher than that of hemorrhagic shock. This may be related to the deleterious effect on cardiac output of the increased blood viscosity of tourniquet shock. Consequently, the high viscosity requires that plasma or plasma substitutes rather than whole blood be the agent of choice for blood volume replacement therapy.

Effective therapy is always accompanied by a substantial reduction in hematocrit and usually by a substantial restoration of the deficiency in plasma volume.

The course of events following ineffective though adequate blood volume replacement therapy of tourniquet shock is not materially altered by the administration of sodium succinate. Cure of five-hour tourniquet shock, attributed by other investigators to succinic acid, is achieved by saline therapy alone in experiments in which anesthesia is omitted. It is therefore apparent that any value sodium succinate may have demonstrated in studies by other investigators may be attributable to its ability to counteract the depressing effect of barbiturates.

AUTHORS.

Blackman, S. S., Jr., Thomas, C. B., and Howard, J. E.: The Effect of Testosterone Propionate on the Arterial Blood Pressure, Kidneys, Urinary Bladder and Livers of Growing Dogs. Bull. Johns Hopkins Hosp. 74: 321, 1944.

Testosterone propionate given subcutaneously to growing puppies of both sexes for periods of six and fourteen weeks produced effects which are well known in other species of animals. The androgen had little effect on the arterial blood pressure of the dogs.

The liver of each treated dog and the kidneys of the dogs treated for fourteen weeks were enlarged by approximately 11 to 17 per cent. The urinary bladders of the treated dogs were considerably enlarged, due probably to hypertrophy of smooth muscle. No effect of the androgen could be detected on the microscopic appearance of the renal juxtaglomerular tissue.

AUTHORS.

Book Reviews

THE ELECTROCARDIOGRAM. ITS INTERPRETATION AND CLINICAL APPLICATION: By Louis H. Sigler, M.D., Attending Cardiologist and Chief of Cardiac Clinics, Coney Island and Harbor Hospitals, New York. Grune & Stratton, Inc., New York, 1944, 400 pages, 203 illustrations.

This ambitious work is divided into twenty-five chapters in which all phases of electrocardiography are taken up. The text is profusely illustrated with diagrams and photographs of many actual electrocardiograms. The latter, except for a small number, are well chosen and satisfactorily reproduced.

The material in the book is not, in the reviewer's opinion, particularly well organized. In many chapters there are discussions and figures relating to electrocardiographic conditions that are treated elsewhere in detail, and Chapter XVI, entitled "Other Abnormalities in the Electrocardiogram," is largely made up of a curious collection of unrelated tracings, practically all of which might logically be presented in other sections of the book. The author discusses multiple precordial leads in some detail in the final chapter, but fails to refer to leads of this type in earlier sections dealing with myocardial infarction, bundle branch block, and ventricular hypertrophy. This arrangement of material may have advantages, but does not properly emphasize the proved value of these leads in the conditions mentioned. Relative to myocardial infarction and ventricular hypertrophy, the reviewer cannot agree with the following statement, made on page 390: In cases of infarction, or in those of ventricular preponderance in which the standard leads show specific changes, there is, as a rule, no need of wasting time in obtaining any of the precordial leads." From the standpoint of diagnosis alone, multiple precordial leads may be unnecessary when one is dealing with infarction. Such leads are, nevertheless, of great value when patients have anterior infarcts because they give information relative to the size of the lesion, and this has obvious bearing on the prognosis. Furthermore, multiple precordial leads are frequently necessary to decide whether right or left axis deviation in the standard leads is due to hypertrophy of the right or left ventricle or is caused by a peculiarity in the position of the heart.

Chapters I and II, concerned with equipment and methods for taking electrocardiograms, are not as complete as could be wished and contain a number of minor inaccuracies.

The discussion of bundle branch block in Chapter XV contains some statements that are open to question. The view of the author that the QRS interval must be over 0.13 second before complete branch block can be considered to be present is certainly not a generally accepted one, and the suggestion that a large part or all of a bundle branch supplying one ventricle must be damaged before complete bundle branch block can occur is not in accord with experimental facts.

The chapters concerned with the cardiac arrhythmias are satisfactory, and the sections dealing with trauma of the heart and the electrocardiogram in various states contain much worth-while material not fully treated in other books on this subject.

The author must be complimented on his conservative attitude, expressed in the preface, relative to the role that the electrocardiogram should play in the diagnosis of heart disease. Although this book cannot be heartily recommended for the dis-

cussions relating to the physical basis of the electrocardiogram or for the fundamental approach that has been employed, it has many attractive features and should be of value to students of electrocardiography.

F. D. JOHNSTON.

A BIBLIOGRAPHY OF AVIATION MEDICINE, SUPPLEMENT: By Phebe Margaret Hoff, Ebbe Curtis Hoff, and John Farquhar Fulton. Committee on Aviation Medicine, Division of Medical Sciences, National Research Council, 1944, 77 pages, plus keys and indexes, 2,336 entries, $2.50.

This supplement brings its rapidly expanding subject up to date, and maintains the high standard of the original *Bibliography* (cf. AM. HEART J. 24: 577, 1942).

HORACE M. KORNS.

Books Received

PUBLICACIONES CEL CENTRO DE INVESTIGACIONES TISIOLOGICAS. Director: Professor Roque A. Izzo. Volume vii, Pabellon "Las Provincias," Buenos Aires, 1943, 462 pages.

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**Executive Committee.*

INDEX TO VOLUME 28

An asterisk (*) after a page number indicates the reference is an abstract and not an original article.

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INDEX NUMBER

Vol. 28 DECEMBER, 1944 No. 6

AMERICAN HEART JOURNAL

For the Study of the CIRCULATION

Published Monthly Under the Editorial Direction of The American Heart Association

Contents on Inside Cover

American Heart Journal

For the Study of the Circulation

CONTENTS FOR DECEMBER, 1944

Original Communications

Clinical Reports

Abstracts and Reviews

Vol. 28, No. 6, December, 1944. American Heart Journal is published monthly by The C. V. Mosby Company, 3523 Pine Blvd., St. Louis, Mo. Subscription Price: United States, its Possessions, Pan-American Countries, $10.00; Canada, $11.50 (Canadian Currency); Foreign, $11.00. Entered as Second-Class Matter at Post Office at St. Louis, Mo., under Act of March 3, 1879. Printed in the U. S. A.

American Heart Journal

For the Study of the Circulation

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